Supplementary Information

Synthesis and biological evaluation of the new ring system benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]-diazepine and its cycloalkane and cycloalkene condensed analogues

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1. Experimental Procedures and Analytical Data

General Methods

^{1}H NMR spectra were recorded at 500.20 MHz, while ^{13}C NMR spectra were measured at 125.62 MHz in $CDCl_3$ or in DMSO-d6 at ambient temperature, with a Bruker AV NEO Ascend 500 spectrometer (Bruker Biospin, Karlsruhe, Germany) with Double Resonance Broad Band Probe (BBO). Chemical shifts are given in δ (ppm), relative to tetramethysilane (TMS) as internal standard. Elemental analyses were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyzer. The HRMS flow injection analysis was performed with Thermo Scientific Q Exactive Plus hybrid quadrupole-Orbitrap (Thermo Fisher Scientific, Waltham, MA, USA) mass spectrometer coupled to a Waters Acquity I-Class UPLC™ (Waters, Manchester, UK). Optical rotations were measured with a Perkin–Elmer 341 polarimeter (Perkin–Elmer, Shelton, CT, USA). Melting points were determined with a Hinotex-X4 micro melting point apparatus (Hinotek, Ningbo, China) and are uncorrected.

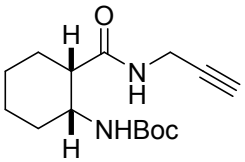
Racemic Boc-protected amino acids [(±)-**1**, (±)-**2**, (±)-**7**, (±)-**8**, (±)-**13**, and (±)-**14**] were prepared according to a literature procedure.[1] Racemic (±)-**15** and (±)-**16** and enantiomers (+)-**15** and (−)-**15** and (±)-**22**, (±)-**23**, (±)-**24**, and (±)-**25** were prepared according to the procedure described in our previous work.[2] 16,16a-dihydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]-diazepino[7,1-*b*]-quinazolin-11(9*H*)-one (**20**) and 6-(prop-2-yn-1-yl)-6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (**21**) were prepared according to a literature procedure.[3,4]

The enantiomers of Boc-protected amino acids (+)-**13** and (−)-**13** were prepared following a previously published work.[2] The *ee* values of (+)-**13**, (−)-**13**, (+)-**15**, and (−)-**15** were determined by a literature method.[2] The *ee* values for (+)-**17a** (84%) and (−)-**17a** (95%) were determined by HPLC using Phenomenex-IA column (eluent: a mixture of *n*-hexane and IPA (60:40), flow rate: 0.5 mL·min^{-1}, detection by PDA detector, retention times (−)-**17a**: 9.98 min, (+)-**17a**: 28.77 min).

The crystals of (±)-**5a**, (±)-**6a**, and (±)-**17c**, were immersed in cryo-oil, mounted in a loop, and measured at a temperature of 120 K. The X-ray diffraction data were collected on a Rigaku Oxford Diffraction Supernova diffractometer using CuKα radiation. *The CrysAlisPro*[5] software package was used for cell refinements and data reductions. An analytical absorption correction (*CrysAlisPro*[5]) was applied to the intensities before structure solutions. The structures were solved by intrinsic phasing (*SHELXT*[6]) method. Structural refinements were carried out using *SHELXL*[6] software with *SHELXLE*[7] graphical user interface. The NH hydrogen atoms were located from the difference Fourier map and refined isotropically. All other hydrogen atoms were positioned geometrically and constrained to ride on their parent atoms, with C-H = 0.95-1.00 Å and U_{iso} = 1.2.U_{eq}(parent atom).

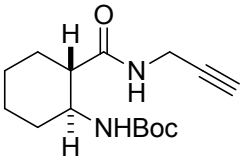
General procedure for the Boc-protected propargyl amide synthesis

A mixture of the appropriate Boc-protected amino acid [**(±)-1, (±)-2, (±)-7, (±)-8, (±)-13, (±)-14, (+)-13** or **(−)-13**, 10 mmol], hydroxybenzotriazole (1.83 g, 12 mmol), *N,N*'-diisopropylcarbodiimide (DIC) (1.51 g, 12 mmol), and propargylamine (0.55 g, 0.7 mL, 10 mmol) was stirred in THF (50 mL) overnight at r.t. After completion of the reaction (checked by thin layer chromatography), the solvent was evaporated. Purification of the residue by column chromatography over silica gel with EtOAc gave the desired products.



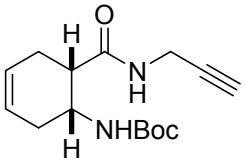
(±)-3

***tert*-Butyl (*cis*-2-(prop-2-yn-1-ylcarbamoyl)cyclohexyl)carbamate (±)-3:** White crystals (84% yield), m.p. 118–121 °C, (R_f = 0.90, EtOAc) ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.43 (s, 9H), 1.54–1.62 (m, 3H), 1.68–1.82 (m, 2H), 1.89–1.97 (m, 1H), 2.50 (t, 1H, *J* = 2.4 Hz), 2.61 (s, 1H), 3.81–3.90 (m, 1H), 3.95–4.09 (m, 2H), 5.27 (d, 1H, *J* = 7.2 Hz), 6.09 (s, 1H); ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 22.7, 26.6, 25.1, 28.3, 29.0, 29.7, 29.9, 44.3, 45.2, 48.9, 71.4, 79.5, 155.7, 173.2 ppm; $C_{15}H_{24}N_2O_3$ (280.36): calcd. C, 64.26; H, 8.63; N, 9.99; found C, 64.05; H, 8.32; N, 9.75. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{15}H_{24}N_2O_3$: 281.18597, found 281.18626.



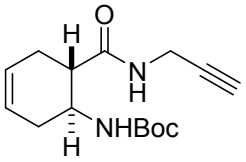
(±)-4

***tert*-Butyl (*trans*-2-(prop-2-yn-1-ylcarbamoyl)cyclohexyl)carbamate (±)-4:** White crystals (84% yield), m.p. 142–145 °C, (R_f = 0.90, EtOAc) ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.18–1.27 (m, 1H), 1.30–1.37 (m, 2H), 1.42 (s, 9H), 1.72–1.79 (m, 2H), 1.93–2.05 (m, 2H), 2.17 (t, 1H, *J* = 2.4 Hz), 2.31 (s, 1H), 3.44–3.53 (m, 1H), 3.93–4.07 (m, 2H), 4.73 (d, 1H, *J* = 8.1 Hz), 6.49 (s, 1H);^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 23.3, 24.9, 25.1, 28.3, 29.1, 30.1, 33.2, 42.5, 51.3, 51.7, 71.2, 79.7, 155.8, 173.8 ppm; $C_{15}H_{24}N_2O_3$ (280.36): calcd. C, 64.26; H, 8.63; N, 9.99; found C, 64.04; H, 8.41; N, 9.87. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{15}H_{24}N_2O_3$: 281.18597, found 281.18597.



(±)-9

***tert*-Butyl (*cis*-6-(prop-2-yn-1-ylcarbamoyl)cyclohex-3-en-1-yl)carbamate (±)-9:** White crystals (74% yield), m.p. 160–163 °C, (R_f = 0.90, EtOAc), ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.44 (s, 1H), 2.09–2.17 (m, 1H), 2.19 (t, 1H, *J* = 2.4 Hz), 2.24–2.32 (m, 1H), 2.38–2.76 (m, 1H), 2.49–2.58 (m, 1H), 2.68–2.74 (m, 1H), 3.97–4.08 (m, 2H), 4.17 (s, 1H), 5.20 (s, 1H), 5.64–5.70 (m, 1H), 5.70–5.77 (m, 1H), 6.69 (s, 1H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 25.5, 28.3, 29.1, 31.4, 43.2, 45.7, 71.3, 79.5, 79.8, 125.1, 125.3, 156.1, 172.6 ppm, $C_{15}H_{22}N_2O_3$ (278.35): calcd. C, 64.73; H, 7.97; N, 10.06; found C, 64.79; H, 8.02; N, 10.10. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{15}H_{22}N_2O_3$: 279,17032, found 279,17086.

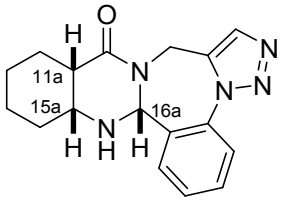


(±)-10

***tert*-Butyl (*trans*-6-(prop-2-yn-1-ylcarbamoyl)cyclohex-3-en-1-yl)carbamate (±)-10:** White crystals (72% yield), m.p. 128–130 °C, (R_f = 0.90, EtOAc), ^{1}H-NMR (500 MHz, $CDCl_3$, 30 °C): δ = 1.43 (s, 1H), 1.71 (s, 1H), 2.18 (t, 1H, *J* = 2.6 Hz), 2.29–2.44 (m, 3H), 2.77 (s, 1H), 3.68–3.77 (m, 1H), 3.95–4.08 (m, 2H), 4.83 (d, 1H, *J* = 7.3 Hz), 5.57–5.63 (m, 1H), 5.63–5.69 (m, 1H), 6.38 (s, 1H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 28.3, 28.8, 29.2, 31.5, 46.6, 48.5, 71.4, 79.5, 79.7, 124.5, 125.3, 155.8, 173.5 ppm, $C_{15}H_{22}N_2O_3$ (278.35): calcd. C, 64.73; H, 7.97; N, 10.06; found C, 64.76; H, 7.98; N, 10.08. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{15}H_{22}N_2O_3$: 279,17032, found 279,17086.

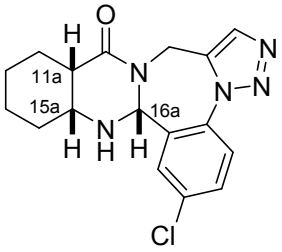
General procedure for domino-ring closure reaction

The mixture of the appropriate Boc-protected amides [**(±)-3, (±)-4, (±)-9, (±)-10, (±)-15, (±)-16, (+)-15** or **(−)-15**, 0.60 mmol] was deprotected by a 10% aqueous HCl solution (10 mL) at r.t. for 6 h. The aqueous layer was neutralized with 10% aqueous NaOH solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried (Na_2SO_4) and the solvent was evaporated. The resulting amides were used in the next step without purification. The appropriate azide derivative (1.2 eq, 0.72 mmol) was added to the free amide in a round-bottom flask equipped with a stir bar and dissolved in EtOH (5 mL, 0.12 M). Iodine (I_2; 15 mg, 0.06 mmol or catalytic amount of *p*-TSA) was added in one portion and the resulting solution was stirred at reflux for 2h. Afterwards, the solvent was evaporated and the crude product was crystalized in Et_2O and recrystallized in *i*Pr_2O–EtOH (5:1, 6 mL).



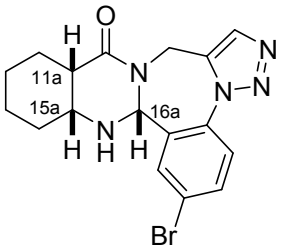
(±)-5a

(*r*-11a,*c*-15a,*c*-16a)-11a,12,13,14,15,15a,16,16a-Octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-5a: Light brown crystals (76% yield), m.p. 170–172 °C, (R_f = 0.45, EtOAc), ^{1}H-NMR (500.20 MHz, DMSO, 30 °C): δ = 1.20–1.32 (m, 2H), 1.37–1.45 (m, 1H), 1.45–1.54 (m, 1H), 1.65–1.75 (m, 4H), 1.77–1.88 (m, 1H), 2.20–2.27 (m, 1H), 3.19 (s, 1H), 3.26 (s, 1H), 3.36 (d, 1H, *J* = 15.4 Hz), 4.99 (d, 1H, *J* = 5.4 Hz), 5.51 (d, 1H, *J* = 15.4 Hz), 7.65–7.72 (m, 1H), 7.81–7.86 (m, 1H), 8.00 (s, 1H), 8.11–8.16 (m, 1H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 20.3, 25.5, 25.8, 34.3, 43.0, 49.9, 69.5, 123.1, 128.6, 129.9, 130.6, 131.5, 133.1, 133.2, 134.8, 171.2 ppm, $C_{17}H_{19}N_5O$ (309.37): calcd. C, 66.00; H, 6.19; N, 22.64; found C, 66.29; H, 6.16; N, 22.44. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{17}H_{19}N_5O$: 310,16624, found 310,16645.



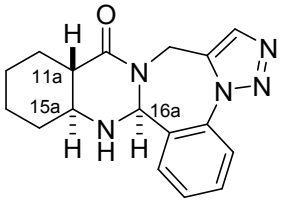
(±)-5b

(*r*-11a,*c*-15a,*c*-16a)-2-Chloro-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-5b: Light brown crystals (73% yield), m.p. 178–183 °C, (R_f = 0.45, EtOAc)**,** ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.30–1.42 (m, 1H), 1.59 (s, 1H), 1.65–1.72 (m, 1H), 1.72–1.80 (m, 2H), 1.84–1.92 (m, 2H), 1.92–2.00 (m, 1H), 2.38–2.44 (m, 1H), 3.32 (s, 1H), 3.65 (d, 1H, *J* = 15.1 Hz), 5.10 (s, 1H), 5.69 (d, 1H, *J* = 15.1 Hz), 7.57–7.62 (m, 1H), 7.77 (s, 1H), 7.84 (d, 1H, *J* = 8.5 Hz), 8.00(d, 1H, *J* = 2.2 Hz), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 20.2, 25.3, 25.9, 30.7, 34.4, 43.2, 50.3, 68.9, 124.5, 127.5, 130.6, 132.2, 132.3, 132.9, 133.4, 135.8, 171.5 ppm, $C_{17}H_{18}ClN_5O$ (343.83): calcd. C, 59.39; H, 5.28; Cl, 10.31; N, 20.37; found C, 59.43; H, 5.29; Cl, 10.33; N, 20.39. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{17}H_{18}ClN_5O$: 344.12726, found 344.12796.



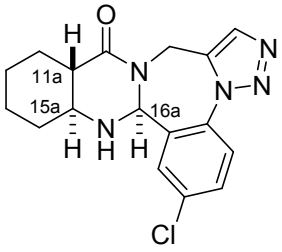
(±)-5c

(*r*-11a,*c*-15a,*c*-16a)-2-Bromo-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-5c: Light brown crystals (72% yield), m.p. 247–252 °C, (R_f = 0.45, EtOAc)**,** ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.30–1.42 (m, 1H), 1.53 (s, 2H), 1.56–1.62 (m, 1H), 1.65–1.81 (m, 4H), 1.82–1.92 (m, 2H), 1.95 (s, 1H), 2.41 (d, 1H, *J* = 12.1 Hz), 3.32 (s, 1H), 3.65 (d, 1H, *J* = 15.3 Hz), 5.10 (s, 1H), 5.69 (d, 1H, *J* = 15.3 Hz), 7.77 (s, 3H), 8.14 (s, 1H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 20.3, 25.3, 25.9, 30.7, 34.4, 40.4, 43.2, 68.9, 123.7, 124.7, 130.5, 132.2, 132.4, 133.0, 133.6, 133.9, 171.5 ppm, $C_{17}H_{18}BrN_5O$ (388.27): calcd. C, 52.59; H, 4.67; N, 18.04; found C, 52.58; H, 4.74; N, 18.12. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{17}H_{18}BrN_5O$: 388,07675, found 388,07745.



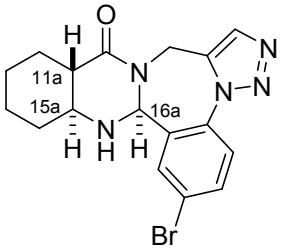
(±)-6a

(*r*-11a,*t*-15a,*t*-16a)-11a,12,13,14,15,15a,16,16a-Octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-6a: Light brown crystals (74% yield), m.p. 178–183 °C, (R_f = 0.45, EtOAc), ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.13–1.23 (m, 1H), 1.28–1.43 (m, 3H), 1.80–1.96 (m, 4H), 2.01–2.08 (m, 1H), 2.37–2.43 (m, 1H), 2.69–2.76 (m, 1H), 3.65 (d, 1H,, *J* = 15.3 Hz), 5.17 (d, 1H, *J* = 5.5 Hz), 5.75 (d, 1H, *J* = 15.3 Hz), 7.57–7.65 (m, 2H), 7.79 (s, 1H), 7.88–7.93 (m, 2H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 24.5, 25.5, 25.7, 32.9, 34.1, 47.6, 56.7, 69.4, 123.3, 126.9, 129.6, 130.2, 130.4, 132.3, 132.8, 134.8, 170.0 ppm, $C_{17}H_{19}N_5O$ (309.37): calcd. C, 66.00; H, 6.19; N, 22.64; found C, 65.92; H, 6.21; N, 22.71. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{19}N_5O$: 310,16624, found 310,16679.



(±)-6b

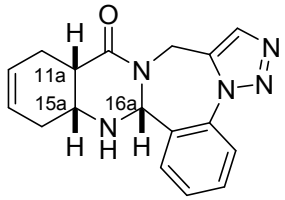
(*r*-11a,*t*-15a,*t*-16a)-2-Chloro-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-6b: Light brown crystals (73% yield), m.p. 198–202 °C, ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.13–1.23 (m, 1H), 1.24–1.35 (m, 3H), 1.80–1.98 (m, 4H), 2.01–2.10 (m, 1H), 2.35–2.42 (m, 1H), 2.68–2.77 (m, 1H), 3.68 (d, 1H,, *J* = 15.2 Hz), 5.68 (s, 1H,), 5.70 (d, 1H, *J* = 15.2 Hz), 7.57–7.61 (m, 1H), 7.77(s, 1H) 7.85 (d, 1H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 2.1 Hz), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 23.4, 24.4, 25.4, 25.6, 32.8, 34.5, 42.1, 47.5. 56.5, 69.1, 124.5, 127.6, 130.6, 132.1, 132.3, 133.0, 133.3, 135.7, 156.9, 169.9 ppm, $C_{17}H_{18}ClN_5O$ (343.83): calcd. C, 59.39; H, 5.28; Cl, 10.31; N, 20.37; found C, 59.33; H, 5.33; Cl, 10.37; N, 20.35. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{18}ClN_5O$: 344,12726, found 344,12737.



(±)-6c

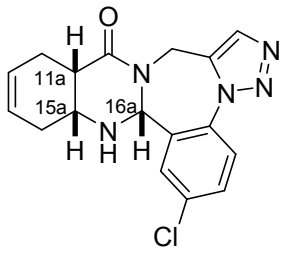
(*r*-11a,*t*-15a,*t*-16a)-2-Bromo-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-6c:

Light brown crystals (69% yield), m.p. 212–218 °C, ^{1}H-NMR (500 MHz, $CDCl_3$, 30 °C): δ = 1.25 (t, 1H), 1.31(t, 2H), 1.36–1.46 (m, 1H), 1.80–1.93 (m, 3H), 2.02–2.09 (m, 2H), 2.38 (d, 1H, *J* = 13.4 Hz), 2.68–2.70 (m, 1H), 3.66 (d, 1H, *J* = 15.1 Hz), 5.14 (s, 1H), 5.70 (d, 1H, *J* = 15.1 Hz), 7.72–7.80 (m, 3H), 8.12 (s, 1H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 20.4, 24.4, 24.8, 25.4, 25.6 32.8, 34.5, 42.1, 47.4, 56.5, 69.0, 123.6, 124.7, 130.6, 132.3, 133.0, 133.5, 133.8, 169.9 ppm, $C_{17}H_{18}BrN_5O$ (388.27): calcd. C, 52.59; H, 4.67; N, 18.04; found C, 52.54; H, 4.75; N, 18.07. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{18}BrN_5O$: 388,07626, found 388,07697.



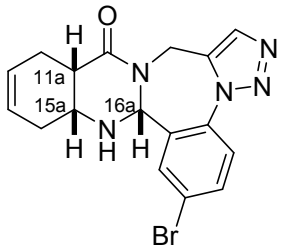
(±)-11a

(*r*-11a,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-Hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-11a: Light brown crystals (77% yield), m.p. 198–203 °C, ^{1}H-NMR (500 MHz, $CDCl_3$, 30 °C): δ = 1.94–2.09 (m, 2H), 2.29–2.38 (m, 1H), 2.45–2.55 (m, 2H), 2.59–2.65 (m, 1H), 3.45 (s, 1H), 3.71 (d, 1H, *J* = 15.2 Hz), 5.19 (s, 1H), 5.65–5.80 (m, 3H), 7.56–7.65 (m, 2H), 7.79 (s, 1H), 7.86–7.92 (m, 2H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 24.8, 30.2, 34.2, 39.1, 48.5, 69.5, 123.3, 123.4, 124.3, 126.8, 129.7, 130.0, 130.5, 132.2, 132.8, 134.8, 171.4 ppm, $C_{17}H_{17}N_5O$ (307.36): calcd. C, 66.43; H, 5.58; N, 22.79; found C, 66.35; H, 5.62; N, 22.76. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{17}N_5O$: 308,15059, found 308,15069.



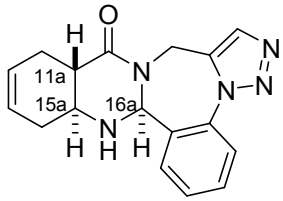
(±)-11b

(*r*-11a,*c*-15a,*c*-16a)-2-Chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-11b: Light brown crystals (71% yield), m.p. 214–217 °C, (R_f = 0.50, EtOAc)**,** ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.60 (s, 1H), 1.89 (s, 1H,), 1.99–2.09 (m, 1H), 2.27–2.39 (m, 1H), 2.43–2.56 (m, 3H), 2.58–2.65 (m, 1H), 3.44 (s, 1H), 3.72 (d, 1H, *J* = 14.4 Hz), 5.17 (s, 1H), 5.66 (d, 1H, *J* = 14.4 Hz), 5.68–5.82 (m, 2H), 7.58–7.62 (m, 1H), 7.78 (s, 1H), 7.85 (d, 1H, *J* = 8.6 Hz), 7.89 (d, 1H, *J* = 2.3 Hz), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 24.8, 28.2, 30.1, 34.3, 35.9, 39.2, 48.5, 69.3, 123.1, 123.5, 124.3, 124.6, 127.4, 130.7, 131.7, 131.8, 132.9, 133.4, 135.8, 171.3 ppm, $C_{17}H_{16}ClN_5O$ (341.79): calcd. C, 59.74; H, 4.72; Cl, 10.37; N, 20.49; found C, 59.77; H, 4.71; Cl, 10.34; N, 20.54. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{16}ClN_5O$: 342,11161, found 342,11145.



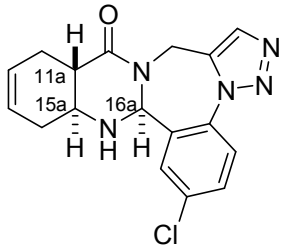
(±)-11c

(*r*-11a,*c*-15a,*c*-16a)-2-Bromo-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-11c: Light brown crystals (71% yield), m.p. 246–248 °C, (R_f = 0.50, EtOAc)**,** ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.59 (s, 1H), 1.89 (s, 1H), 1.98–2.09 (m, 1H), 2.27–2.38 (m, 1H), 2.43–2.56 (m, 2H), 2.58–2.65 (m, 1H), 3.44 (s, 1H), 3.73 (d, 1H, *J* = 15.4 Hz), 5.17 (s, 1H), 5.66 (d, 1H, *J* = 15.4 Hz), 5.68–5.82 (m, 2H), 7.73–7.80 (m, 3H), 8.04 (d, 1H, *J* = 1.9 Hz),^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 24.8, 30.1, 34.3, 39.2, 48.6, 69.3, 123.1, 123.7, 124.3, 124.6, 124.8, 130.0, 132.2, 132.9, 133.7, 133.8, 171.2 ppm, $C_{17}H_{16}BrN_5O$ (386.25): calcd. C, 52.86; H, 4.18; N, 18.13; found C, 52.81; H, 4.15; N, 18.05. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{16}BrN_5O$: 386,06110, found 386,06188.



(±)-12a

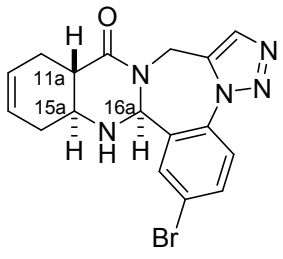
(*r*-11a,*t*-15a,*t*-16a)-11a,12,15,15a,16,16a-Hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-12a: Light brown crystals (75% yield), m.p. 195–199 °C, ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 2.00–2.20 (m, 3H), 2.35–2.43 (m, 2H), 3.02–3.10 (m, 1H), 3.68 (d, 1H, *J* = 15.3 Hz), 5.20 (d, 1H, *J* = 6.4 Hz), 5.62–5.81 (m, 3H), 7.56–7.67 (m, 2H), 7.80 (s, 1H), 7.88–7.94 (m, 2H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 26.5, 32.5, 34.2, 43.4, 53.1, 69.3, 123.4, 124.0, 126.7, 126.9, 129.7, 129.8, 130.5, 132.2, 132.8, 134.8, 169.8 ppm, $C_{17}H_{17}N_5O$ (307.36): calcd. C, 66.43; H, 5.58; N, 22.79; found C, 66.48; H, 5.56; N, 22.82. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{17}N_5O$: 308,15059, found 308,15078.



(±)-12b

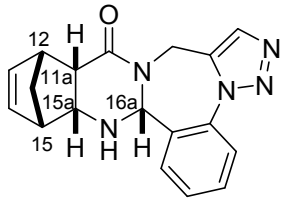
(*r*-11a,*t*-15a,*t*-16a)-2-Chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-12b: Light brown crystals (68% yield), m.p. 201–205 °C, ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.97–2.13 (m, 2H), 2.13–2.23 (m, 1H), 2.67–2.75 (m, 1H), 3.02–3.10 (m, 1H), 3.70 (d, 1H, *J* = 15.2 Hz), 5.19 (s, 1H),

5.62–5.79 (m, 3H), 7.58–7.62 (m, 1H), 7.79 (s, 1H), 7.85 (d, 1H, *J* = 8.5 Hz), 7.94 (d, 1H, *J* = 2.2 Hz), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 23.4, 26.4, 32.4, 34.3, 42.2, 43.3, 53.0, 69.0, 123.9, 124.6, 126.7, 126.6, 127.6, 129.8, 130.6, 131.7, 132.3, 132.9, 133.3, 135.8, 169.7 ppm, $C_{17}H_{16}ClN_5O$ (341.79): calcd. C, 59.74; H, 4.72; Cl, 10.37; N, 20.49; found C, 59.76; H, 4.78; Cl, 10.33; N, 20.46. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{16}ClN_5O$: 342,11161, found 342,11193.



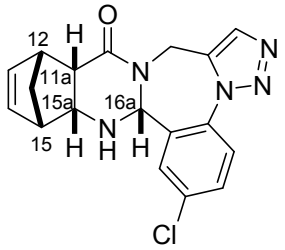
(±)-12c

(*r*-11a,*t*-15a,*t*-16a)-2-Bromo-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-b]quinazolin-11(9*H*)-one (±)-12c: Light brown crystals (66% yield), m.p. 218–223 °C, ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 2.01–2.24 (m, 4H), 2.66–2.74 (m, 1H), 3.02–3.10 (m, 1H), 3.69 (d, 1H, *J* = 15.3 Hz), 5.18 (s, 1H), 5.63–5.79 (m, 3H), 7.74–7.80 (m, 3H), 8.10 (s, 1H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 23.5, 26.4, 32.3, 34.3, 42.1, 43.2, 52.9, 68.9, 123.7, 124.0, 124.8, 126.6, 130.6, 131.8, 132.2, 133.0, 133.6, 133.7, 169.8 ppm, $C_{17}H_{16}BrN_5O$ (386.25): calcd. C, 52.86; H, 4.18; N, 18.13; found C, 52.78; H, 4.16; N, 18.16. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{17}H_{16}BrN_5O$: 386,06110, found 386,06190.



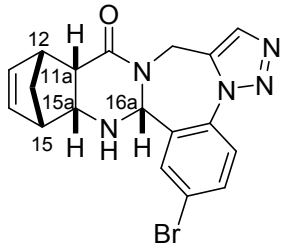
(±)-17a

(*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-Hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-17a: Light brown crystals (70% yield), m.p. 213–216 °C, (R_f = 0.40, EtOAc), ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.25 (t, 2H, *J* = 7.1 Hz), 1.48 (d, 1H, *J* = 9.1 Hz), 1.60 (s, 1H), 1.63 (d, 1H, *J* = 9.1 Hz), 2.63–2.68 (m, 1H), 3.19 (s, 1H), 3.48 (s, 1H), 3.89–3.95 (m, 1H), 5.26 (s, 1H), 6.17 (s, 1H), 6.45 (s, 1H), 7.53–7.64 (m, 2H), 7.72 (d, 1H, *J* = 7.9 Hz), 7.74 (s, 1H), 7.83 (d, 1H, *J* = 7.9 Hz), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 33.3, 44.4, 46.4, 46.6, 47.6, 58.3, 124.2, 128.7, 129.5, 130.5, 131.4, 132.0, 133.1, 133.2, 134.5, 140.4, 171.0 ppm, $C_{18}H_{17}N_5O$ (319.37): calcd. C, 67.70; H, 5.37; N, 21.93; found C, 67.67; H, 5.41; N, 21.96. HRMS-ESI $[M+H]^+$*m/z* calcd for $C_{18}H_{17}N_5O$: 320,15059, found 320,15132.



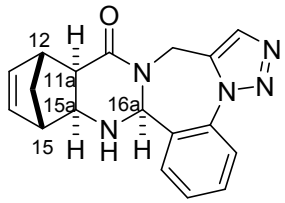
(±)-17b

(*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-Chloro-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-17b: Light brown crystals (69% yield), m.p. 250–253 °C, (R_f = 0.40, EtOAc), ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.48 (d, 1H, *J* = 9.0 Hz), 1.65 (d, 1H, *J* = 9.0 Hz), 2.63–2.68 (m, 1H), 3.21 (s, 1H), 3.48 (s, 1H), 3.91 (s, 2H), 5.22 (s, 1H), 5.59 (s, 1H), 6.22 (s, 1H), 6.47 (s, 1H), 7.56–7.60 (m, 1H), 7.72–7.80 (m, 3H), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 33.1, 44.5, 46.4, 46.6, 47.6, 58.3, 125.4, 128.9, 130.3, 130.6, 131.6, 132.9, 133.1, 133.1, 135.6, 140.5, 170.9 ppm, $C_{18}H_{16}ClN_5O$ (353.81): calcd. C, 61.10; H, 4.56; Cl, 10.02; N, 19.79; found C, 61.07; H, 4.55; Cl, 10.10; N, 19.81. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{18}H_{16}ClN_5O$: 354,11161, found 354,11197.



(±)-17c

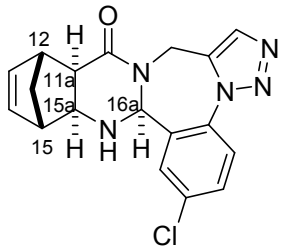
(*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-Bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-17c: Light brown crystals (62% yield), m.p. 258–261 °C, (R_f = 0.40, EtOAc), ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.45 (d, 1H, *J* = 9.1 Hz), 1.65 (d, 1H, *J* = 9.1 Hz), 2.63–2.68 (m, 1H), 3.21 (s, 1H), 3.48 (s, 1H), 3.90 (s, 2H), 5.22 (s, 1H), 5.58 (s, 1H), 6.22 (s, 1H), 6.46 (s, 1H), 7.68–7.76 (m, 3H), 7.90 (s, 1H), ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ = 29.6, 33.8, 41.2, 44.3, 44.3, 45.7, 47.9, 57.0, 123.4, 125.7, 130.7, 131.7, 131.8, 133.2, 133.8, 135.2, 138.6, 170.9 ppm, $C_{18}H_{16}BrN_5O$ (398.26): calcd. C, 54.28; H, 4.05; N, 17.59; found C, 54.31; H, 3.98; N, 17.58. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{18}H_{16}BrN_5O$: 398,0611, found 398,06063.



(±)-18a

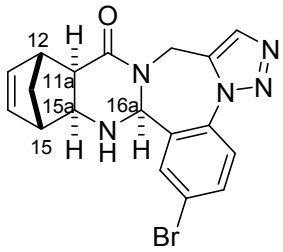
(*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-Hexahydro-12,15 methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]-quinazolin-11(9*H*)-one (±)-18a:

Light brown crystals (68% yield), m.p. 217–220 °C, (R_f = 0.40, EtOAc)**,** ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.20 (t, 2H, *J* = 6.9 Hz), 1.50 (s, 2H), 2.13 (d, 1H, *J* = 7.7 Hz), 2.86 (s, 1H), 3.24 (d, 1H, *J* = 7.7 Hz), 3.45–3.51 (m, 2H), 4.00 (s, 1H), 5.29 (s, 1H), 6.12 (s, 1H), 6.30 (m, 1H), 7.58 (t, 1H, *J* = 7.0 Hz), 7.64 (t, 1H, *J* = 7.0 Hz), 7.77 (s, 2H,), 7.89 (d, 1H, *J* = 7.9 Hz), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 23.5, 34.0, 42.2, 44.2, 44.3, 45.6, 47.6, 124.4, 128.9, 129.6, 130.7, 131.6, 134.7, 135.3, 138.6, 171.1 ppm**,** $C_{18}H_{17}N_5O$ (319.37): calcd. C, 67.70; H, 5.37; N, 21.93; found C, 67.66; H, 5.35; N, 21.96. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{18}H_{17}N_5O$: 320,15059, found 320,15121.



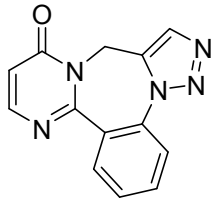
(±)-18b

(*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-2-Chloro-11a,12,15,15a,16,16a-hexa-hydro-12,15-methanobenzo[5,6][1,2,3]triazolo-[5',1':3,4][1,4]-diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-18b : Light brown crystals (69% yield), m.p. 252–246 °C, ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.10–1.68 (m, 2H), 2.13 (d, 1H, *J* = 6.2 Hz), 2.90 (s, 1H), 3.23 (d, 1H, *J* = 6.2 Hz), 3.50 (s, 1H), 5.23 (s, 1H), 6.11–6.14 (m, 1H), 6.28–6.31 (m, 1H), 7.60 (d, 1H, *J* = 7.9 Hz), 7.75 (s, 1H), 7.79 (s, 1H), 7.83 (d, 1H, *J* = 8.3 Hz) ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 33.9, 44.3, 44.3, 45.7, 48.0, 57.0,125.6, 129.0, 130.6, 130.8, 131.7, 133.3, 135.3, 135,6, 138.7, 170.9 ppm, $C_{18}H_{16}ClN_5O$ (353.81): calcd. C, 61.10; H, 4.56; Cl, 10.02; N, 19.79; found C, 61.06; H, 4.60; Cl, 10.04; N, 19.81. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{18}H_{16}ClN_5O$: 354,11161, found 354,11197.



(±)-18c

(*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-2-Bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]-diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-18c: Light brown crystals (64% yield), m.p. 260–264 °C, ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 1.52 (s, 2H), 2.12 (d, 1H, J = 7.6 Hz), 2.89 (s, 1H), 3.23 (d, 1H, J = 7.6 Hz), 3.49 (s, 1H), 5.23 (s, 1H), 6.11–6.14 (m, 1H), 6.28–6.31 (m, 1H), 7.73–7.78 (m, 3H), 7.94 (s, 1H) ^{13}C NMR (125.62 MHz, CDCl3, 30 °C): δ = 29.6, 33.8, 41.2, 44.3, 44.3, 45.7, 47.9, 57.0, 123.4, 125.7, 130.7, 131.7, 131.8, 133.2, 133.7, 133.8, 135.2, 138.6, 170.9 ppm, $C_{18}H_{16}BrN_5O$ (398.26): calcd. C, 54.28; H, 4.05; N, 17.59; found C, 54.26; H, 4.03; N, 17.61. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{18}H_{16}BrN_5O$: 398,06110, found 398,06051.

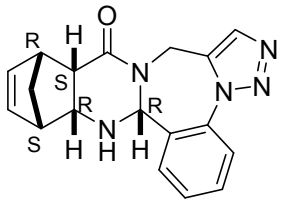


19

9*H*-Benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-11-one 19: Light brown crystals (66% yield), m.p. 287–291 °C, (R_f = 0.50, EtOAc)**,** ^{1}H-NMR (500.20 MHz, $CDCl_3$, 30 °C): δ = 4.20 (d, 1H, *J* = 15.0 Hz), 6.50 (d, 1H, *J* = 6.5 Hz), 6.60 (d, 1H, *J* = 15.0 Hz), 7.67 (t, 1H, *J* = 8.0 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 7.89 (s, 1H), 7.99 (d, 1H, *J* = 6.5 Hz) 8.11 (d, 1H, *J* = 8.0 Hz), 8.22 (d, 1H, *J* = 8.0 Hz), ^{13}C NMR (125.62 MHz, $CDCl_3$, 30 °C): δ = 33.5, 113.7, 123.3, 125.7, 129.3, 132.1, 132.6, 133.4, 133.6, 133.8, 152.9, 157.0, 160.0 ppm**,** $C_{13}H_9N_5O$ (251.25): calcd. C, 62.15; H, 3.61; N, 27.87; found C, 62.07; H, 3.41; N, 27.93. HRMS-ESI $[M+H]^+$*m*/*z* calcd for $C_{13}H_9N_5O$: 252,08799, found 252,08838.

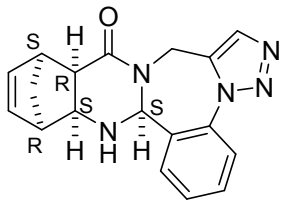
Representative Data for the enantiomerically pure compounds (+)-17a and (–)-17a

^{1}H and ^{13}C NMR data of the enantiomeric compounds were identical with those of the racemic compounds



(+)-17a

(11a*S*,12*R*,15*S*,15a*R*,16a*R*)-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (+)-17a: Light brown crystals (70% yield), m.p. 213–216 °C, (R_f = 0.40),$[\alpha]_D^{25}$ = +61 (c = 0.5, EtOH)



(-)-17a

(11a*R*,12*S*,15*R*,15a*S*,16a*S*)-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (–)-17a: Light brown crystals (70% yield), m.p. 213–216 °C, (R_f = 0.40),$[\alpha]_D^{25}$ = –63 (c = 0.5, EtOH)

Determination of antiproliferative activities

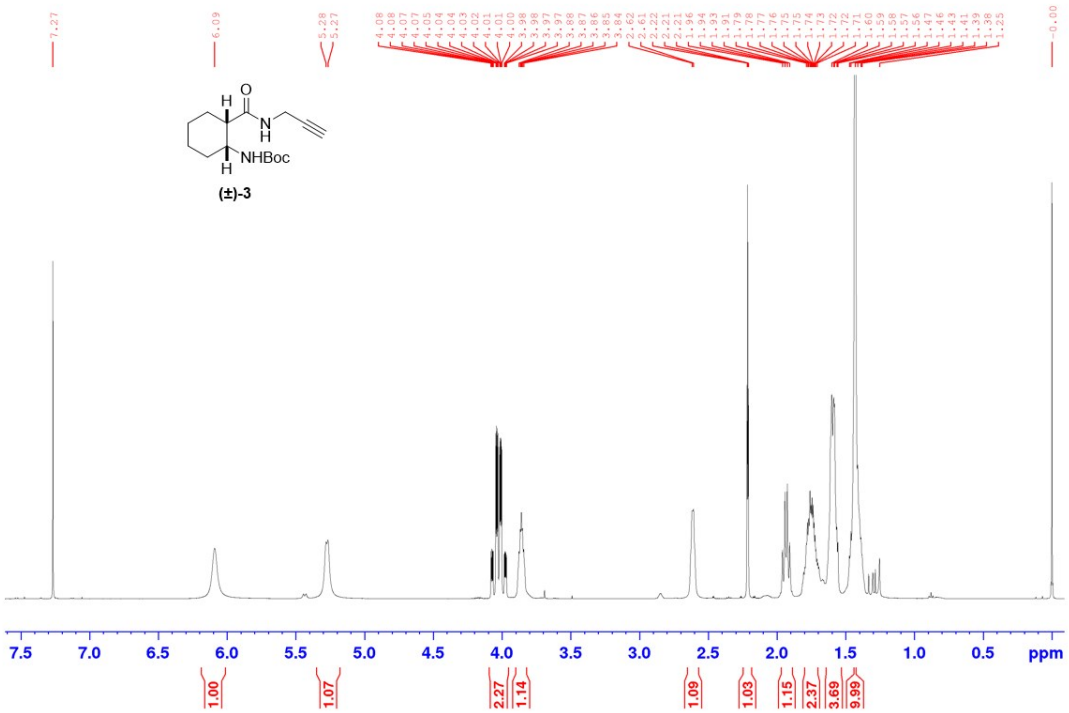
The effects of the tested compounds on cell growth were determined using a standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay on a selection of human gynaecological cancer cell lines of epidemiological significance: MCF-7 (ER+, PR+, and HER2- breast cancer), MDA-MB-231 (ER-, PR- and HER2- breast cancer), HeLa (human papilloma virus [HPV] 18 positive cervical cancer), SiHa (HPV 16 positive cervical cancer) and A2780 (ER- ovarian cancer)[8]. The cell lines – apart from SiHa – were obtained from ECACC (European Collection of Cell Cultures, Salinsbury, UK). SiHa was obtained from ATCC (American Tissue Culture Collection, Manassas, VA, USA). Cells were propagated in minimal essential medium supplemented with 10% fetal bovine serum, 1% non-essential amino acids and a 1% penicillin–streptomycin mixture at 37 °C in a humidified atmosphere containing 5% CO_2. All media and culture supplements were purchased from Lonza Group Ltd. (Based, Switzerland).

Cells were seeded into 96-well microtiter plates (at a cell density of $5x10^3$/well) and incubated with the tested compounds at 10 µM and 30 µM under cell-culture conditions for 72 h. Subsequently, the MTT solution (5 mg/mL) was added to each well, which were further incubated for 4 h. The medium was removed and the precipitated formazan crystals were dissolved in 0.1 mL DMSO during a 1 h shaking at 37 °C.[8] The absorbance in the wells was measured at 545 nm using a microplate reader. Untreated cells served as controls during the measurements. Results presented in the paper have been obtained from two independent experiments with five wells per each condition. Cisplatin (Ebewe Pharmaceuticals, Unterach, Austria) was used a reference agent. Calculations were performed using GraphPad Prism 5.01 software (GraphPad Software Inc., San Diego, CA, USA).

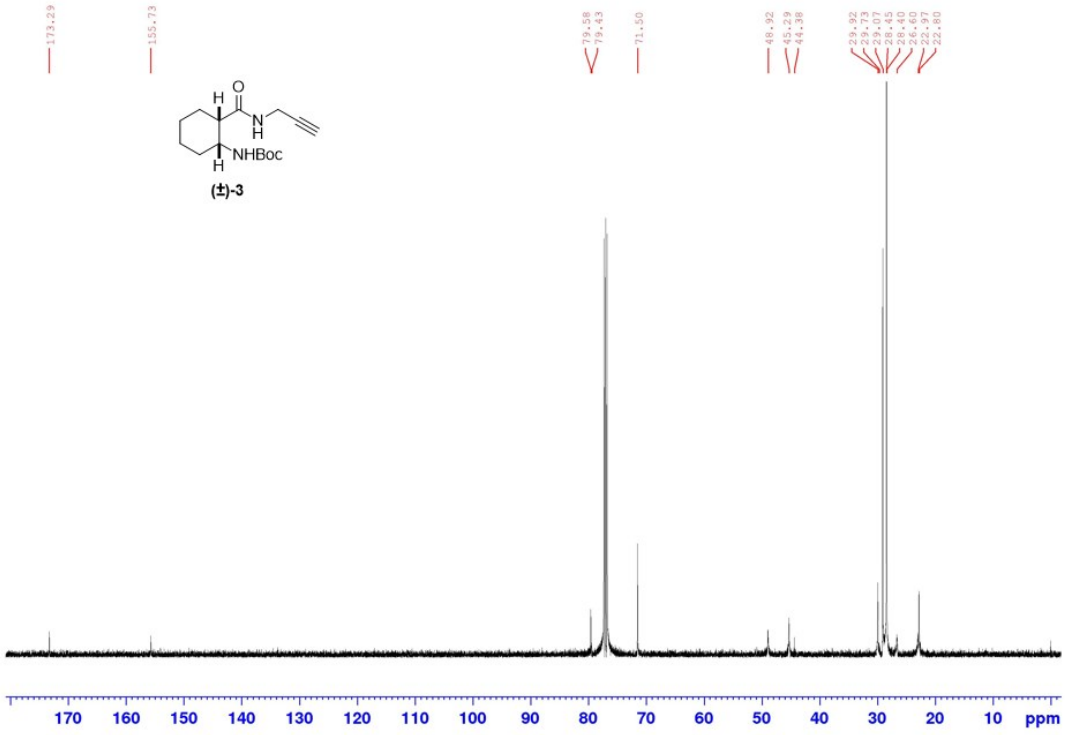
2. Refences

1 F. Fülöp, M. Palkó, E. Forró, M. Dervarics, T.A. Martinek, R. Sillanpää, *Eur. J. Org. Chem.* 2005, **15**, 3214–3220.
2 M. Palkó, M. El Haimer, Z. Kormányos, F. Fülöp, *Molecules* 2019, **24**, 772.
3 K. G. Guggenheim, H. Toru, M. J. Kurth, *Org. Lett*. 2012, **14**, 3732-3735.
4 M. V. Madhubabu, R. Shankar, G. R. Reddy, T. S. Rao, M. V. B. Rao, R. Akula*, Tetrahedron Lett*. 2016, **46**, 5033-5037.
5 Rikagu Oxford Diffraction, CrysAlisPro, Agilent Technologies inc., 2018, Yarnton, Oxfordshire, England.
6 G. M. Sheldrick, *Acta Cryst.* 2015, **71**, 3-8.
7 C. B. Hübschle, G. M. Sheldrick, B. Dittrich, *J. Appl. Cryst*. 2011, **44**, 1281-1284.
8 D. Ozsvár, V. Nagy, I. Zupkó, Z. Szakonyi, *Int. J. Mol. Sci*. 2019, **21**, e184.

3. Copies of ^{1}H- and ^{13}C NMR spectra of (±)-3 - 19



^{1}H NMR Spectrum of *tert*-butyl (*cis*-2-(prop-2-yn-1-ylcarbamoyl)cyclohexyl)carbamate **(±)-3** ($CDCl_3$)



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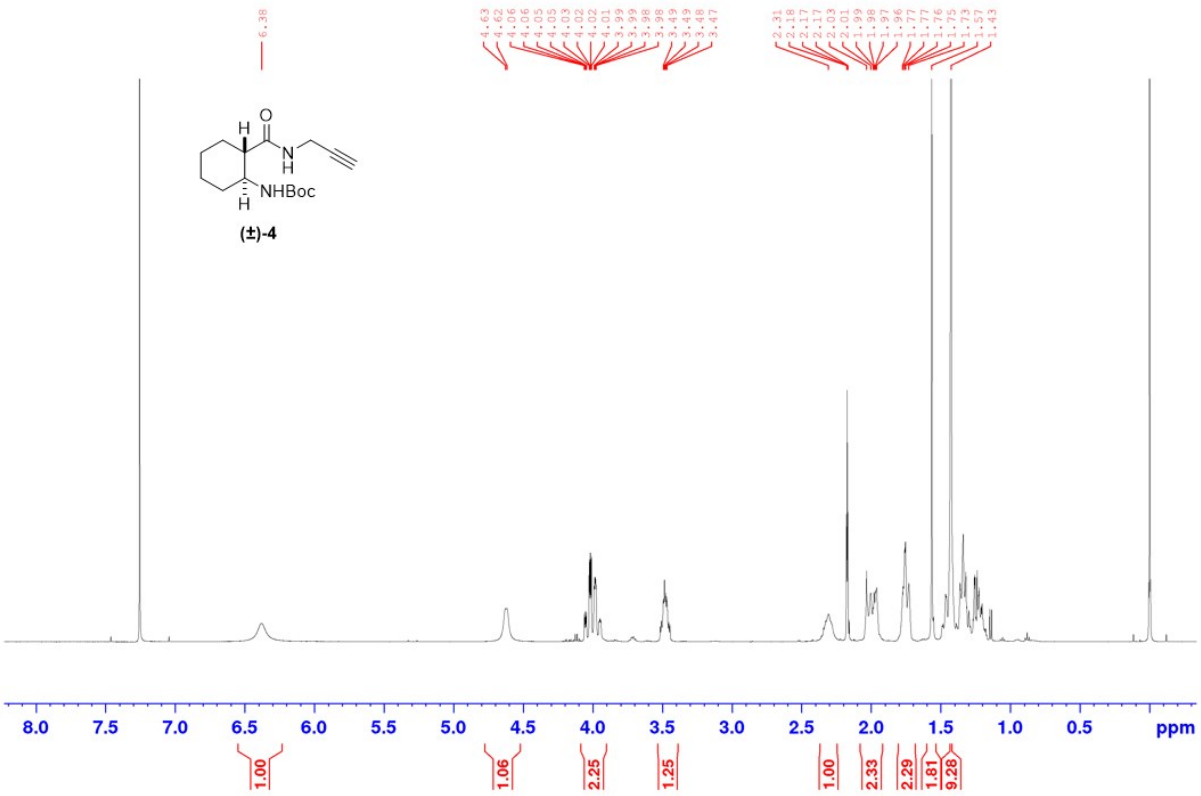

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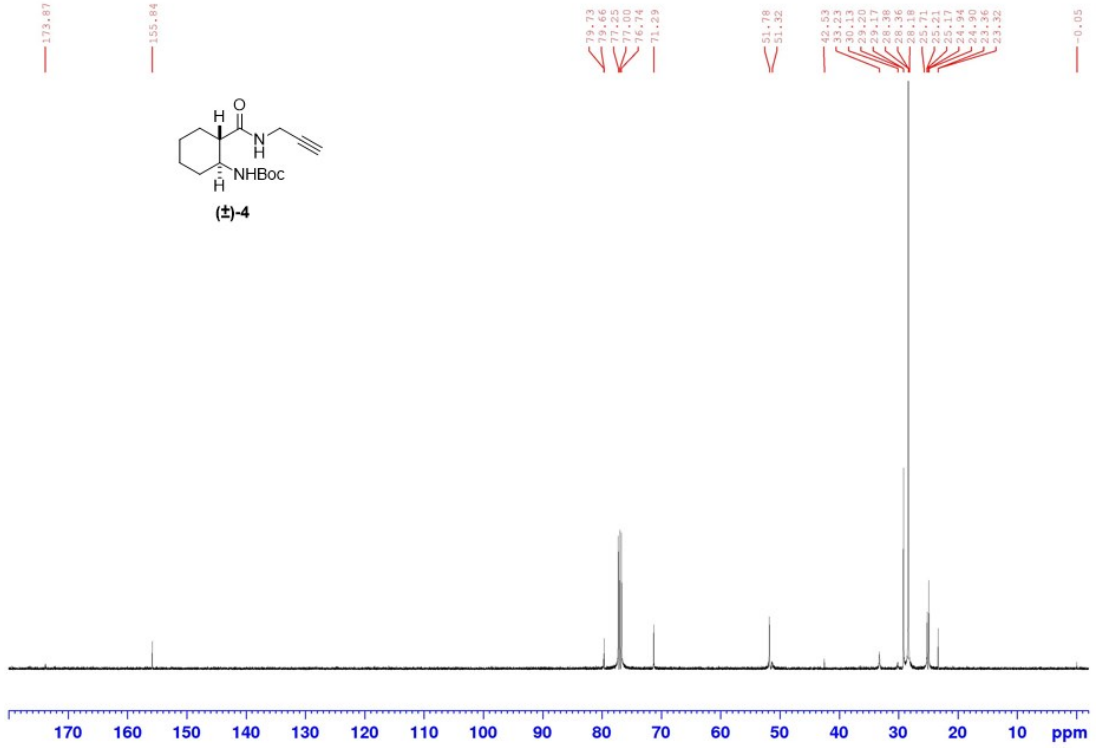
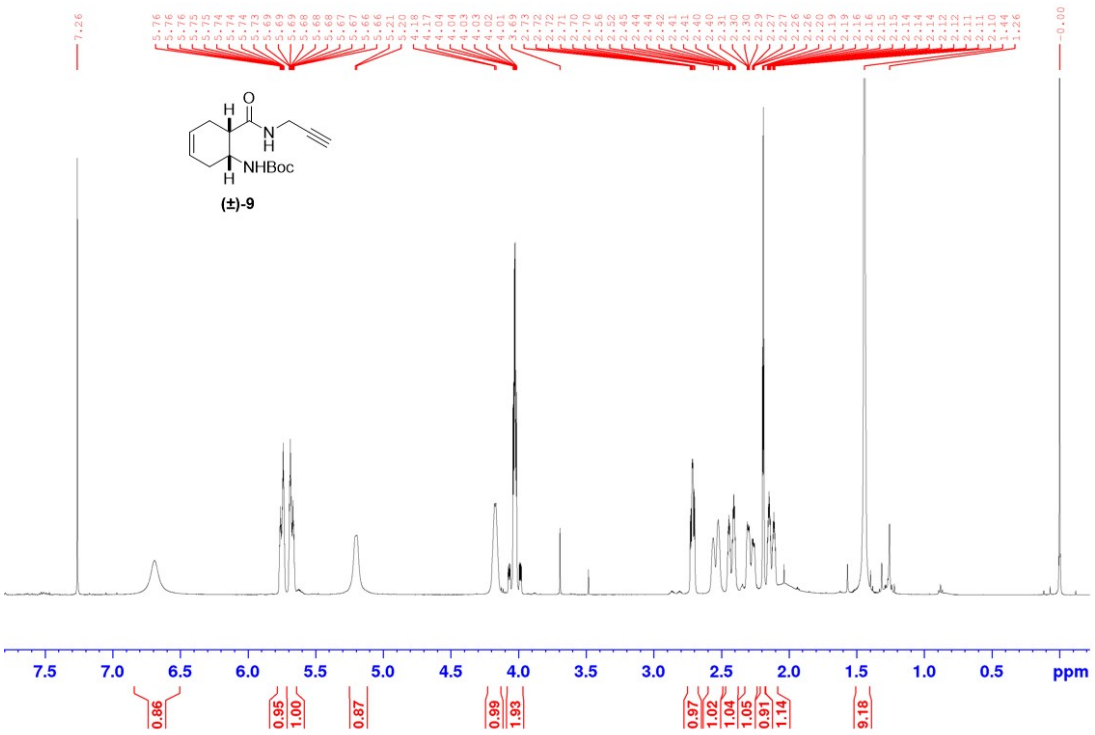
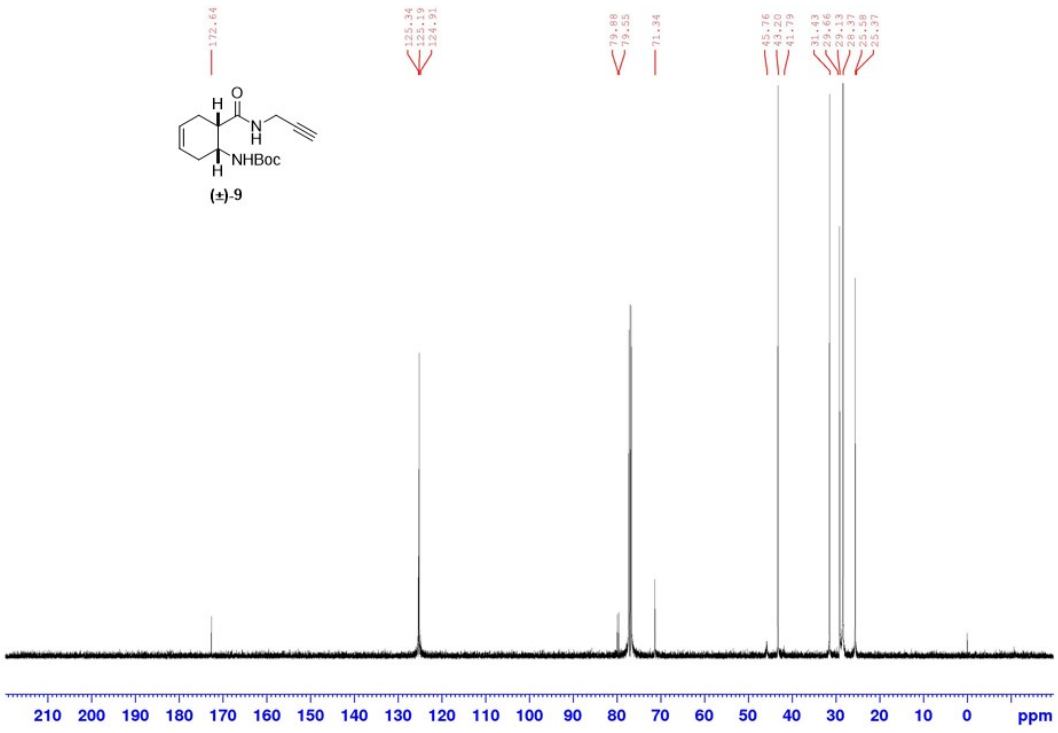


^{13}C NMR Spectrum of *tert*-butyl (*trans*-2-(prop-2-yn-1-ylcarbamoyl)cyclohexyl)carbamate **(±)-4** ($CDCl_3$)



^{1}H NMR Spectrum of *tert*-butyl (*cis*-6-(prop-2-yn-1-ylcarbamoyl)cyclohex-3-en-1-yl)carbamate **(±)-9** ($CDCl_3$)



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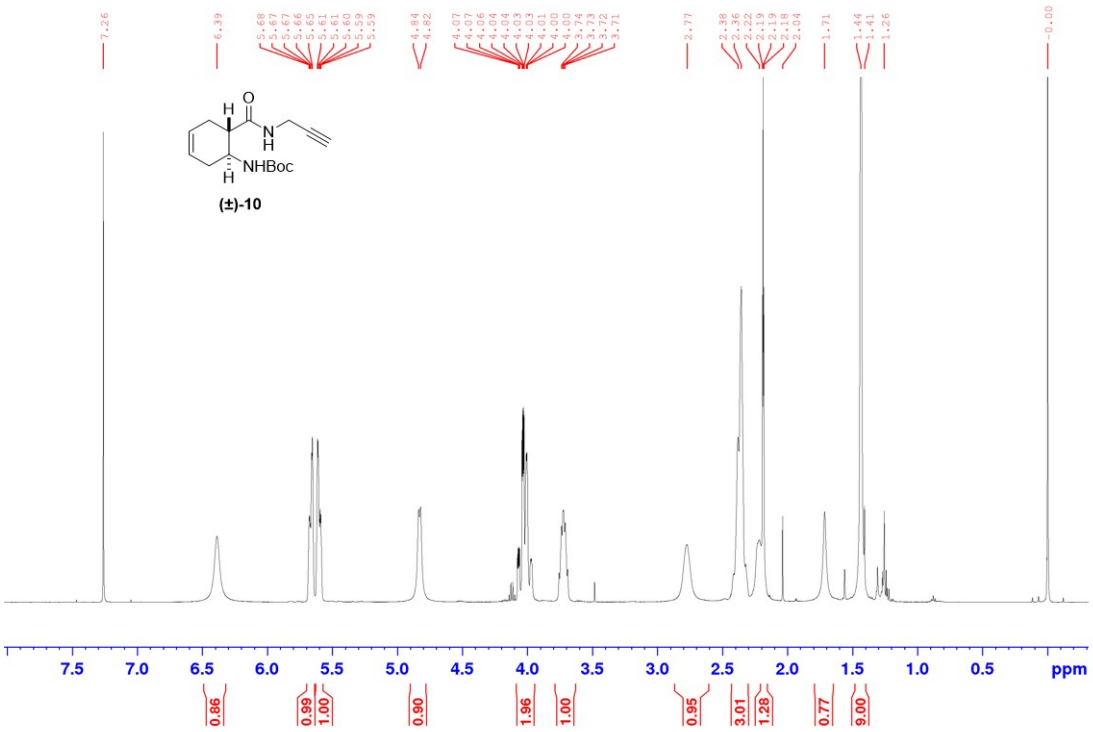

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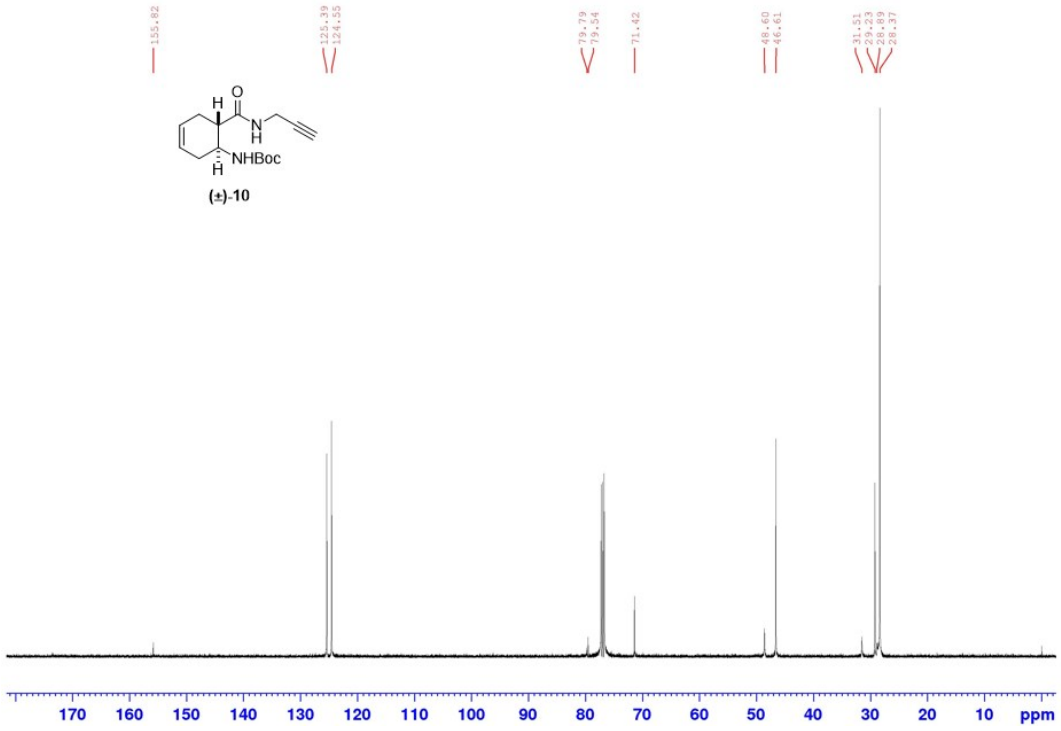

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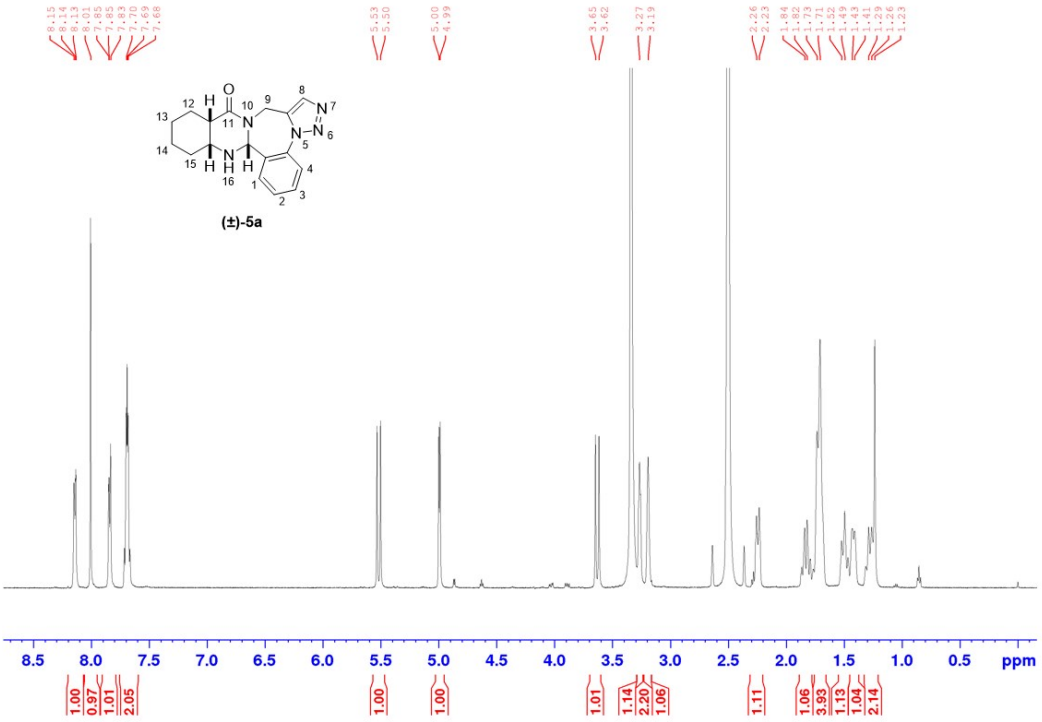
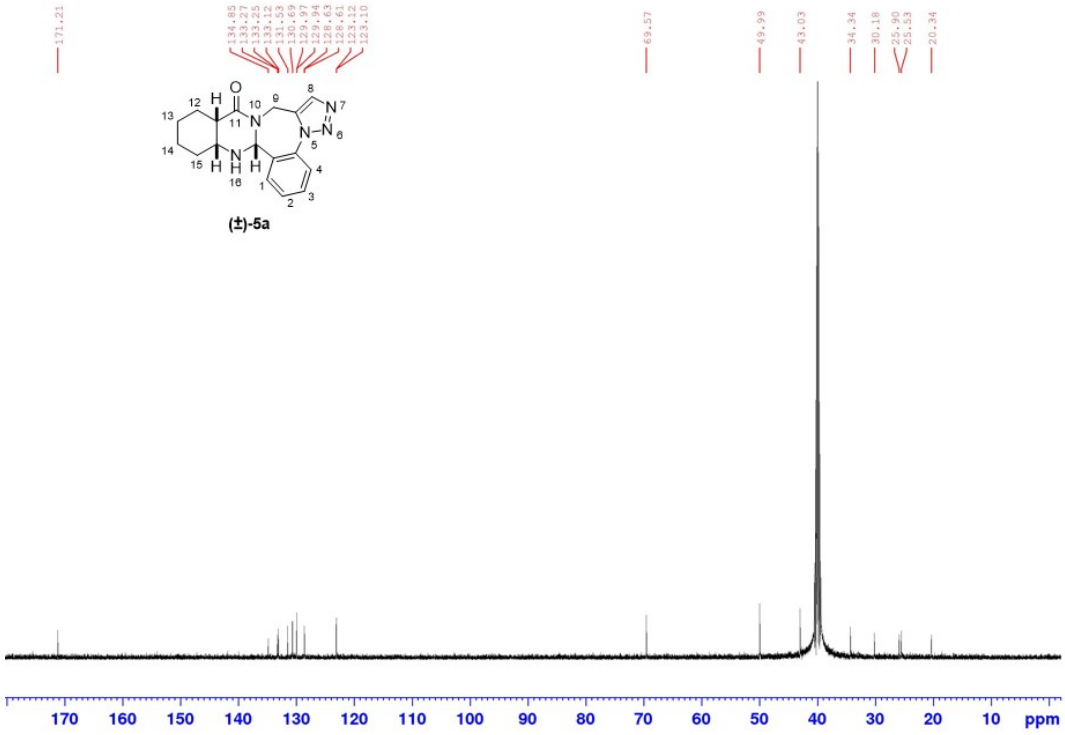
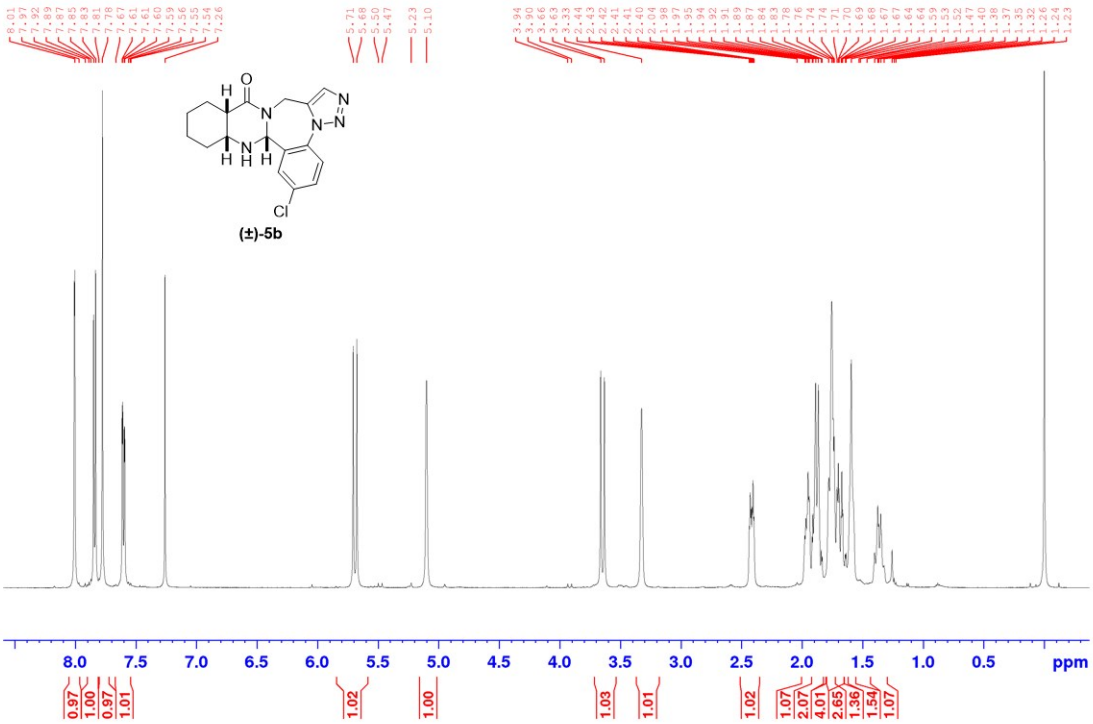


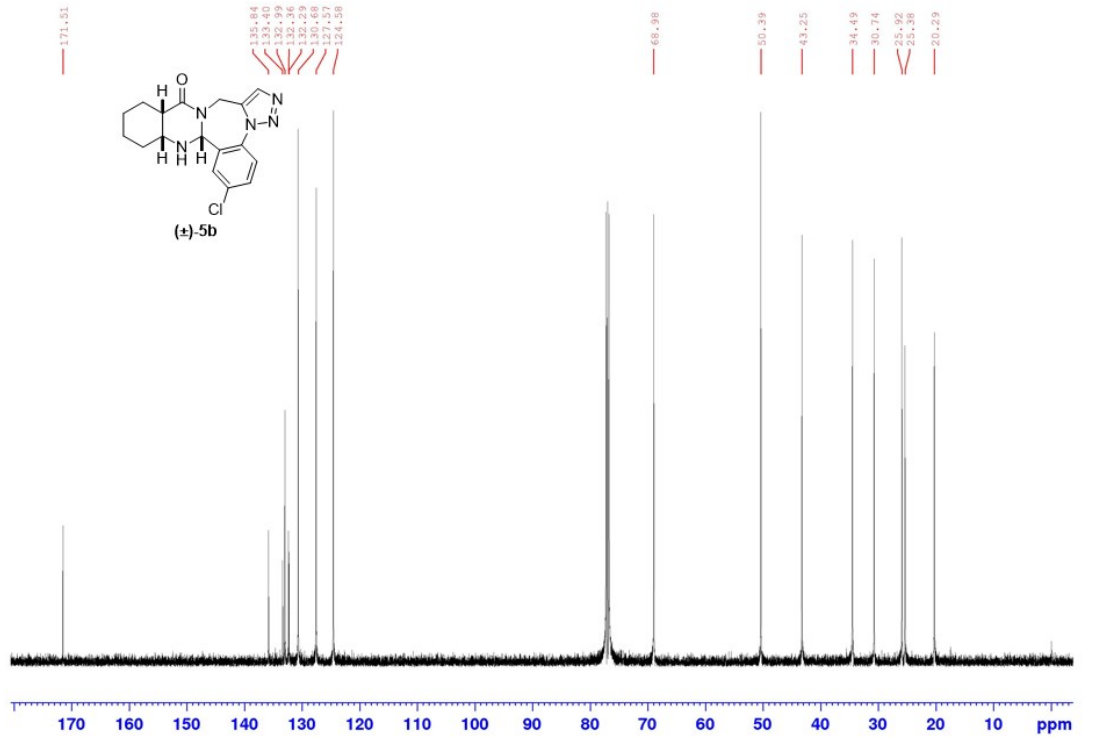
^{1}H NMR Spectrum of (*r*-11a,*c*-15a,*c*-16a)-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-5a**: (DMSO)



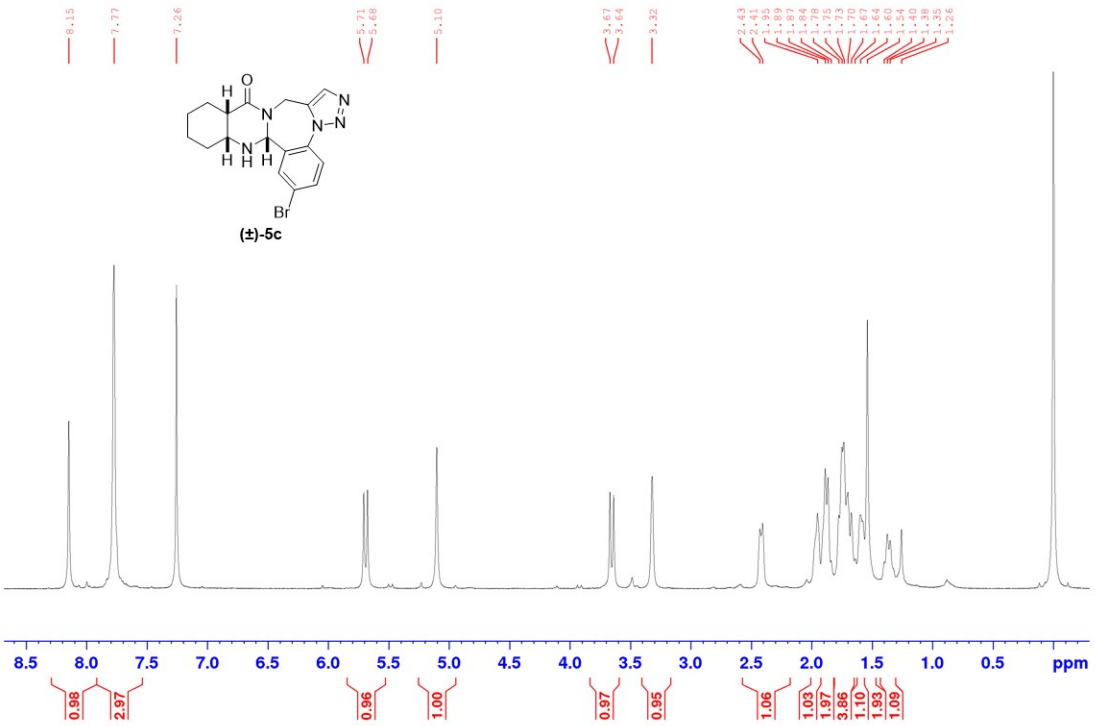
^{13}C NMR Spectrum of (*r*-11a,*c*-15a,*c*-16a)-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-5a**: (DMSO)



^{1}H NMR Spectrum of (*r*-11a,*c*-15a,*c*-16a)-2-chloro-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-5b** ($CDCl_3$)



^{13}C NMR Spectrum of (*r*-11a,*c*-15a,*c*-16a)-2-chloro-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-5b** ($CDCl_3$)



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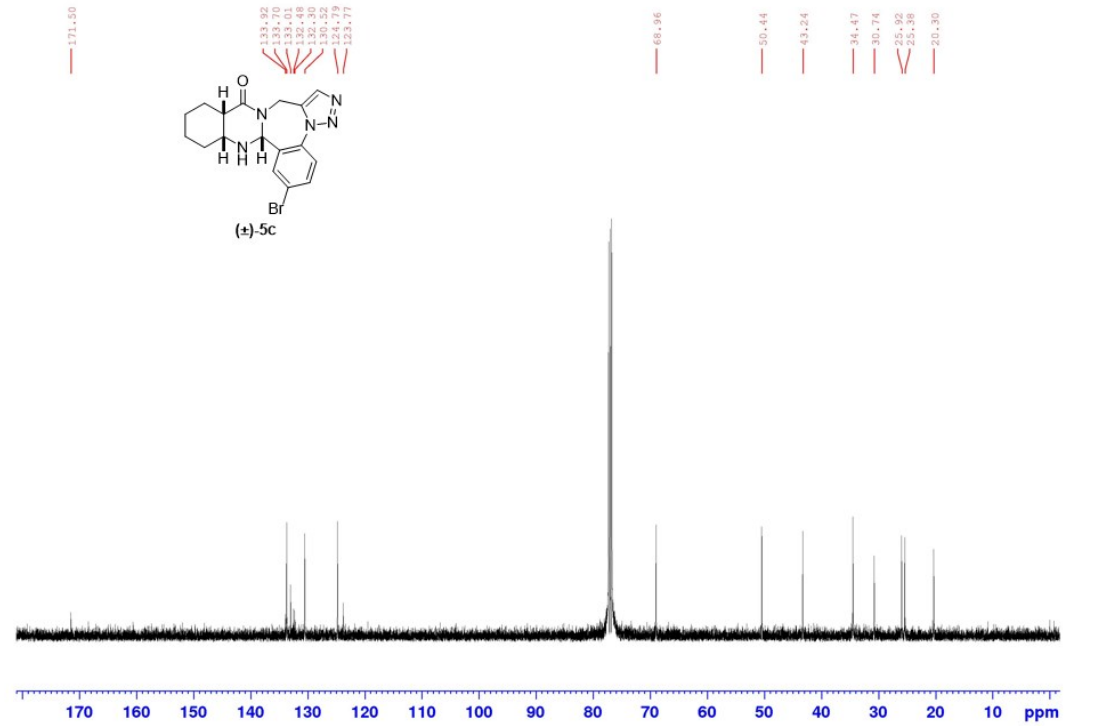
^{1}H NMR Spectrum of (*r*-11a,*c*-15a,*c*-16a)-2-bromo-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-5c** ($CDCl_3$)



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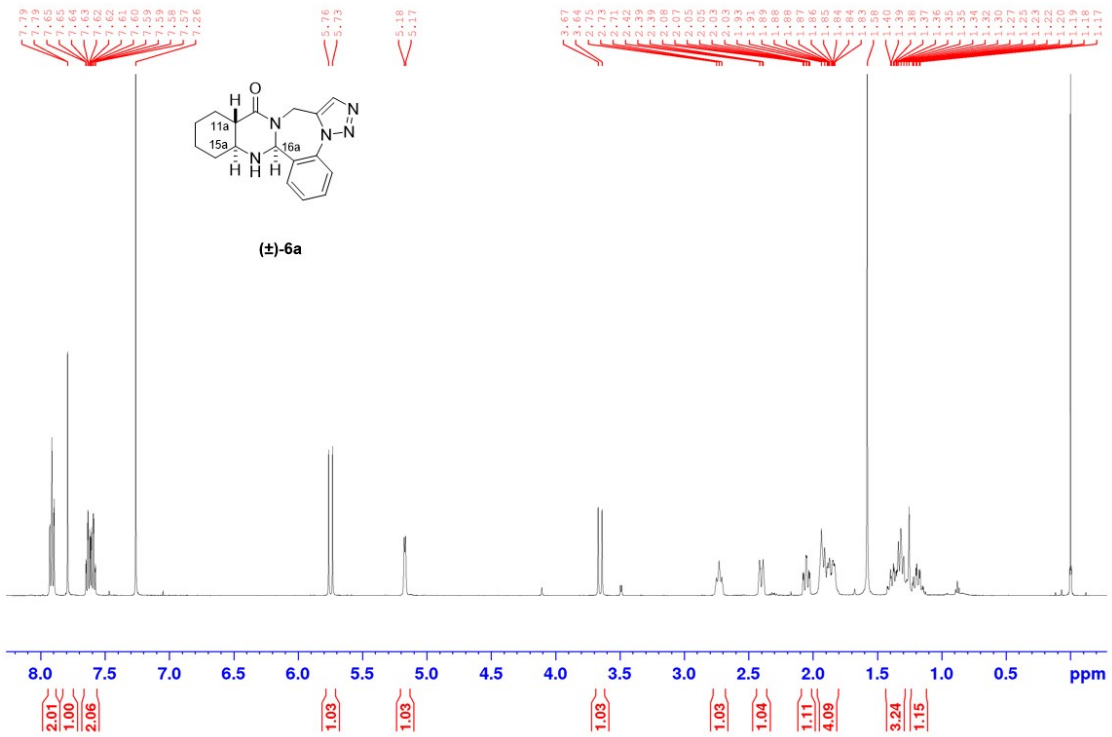

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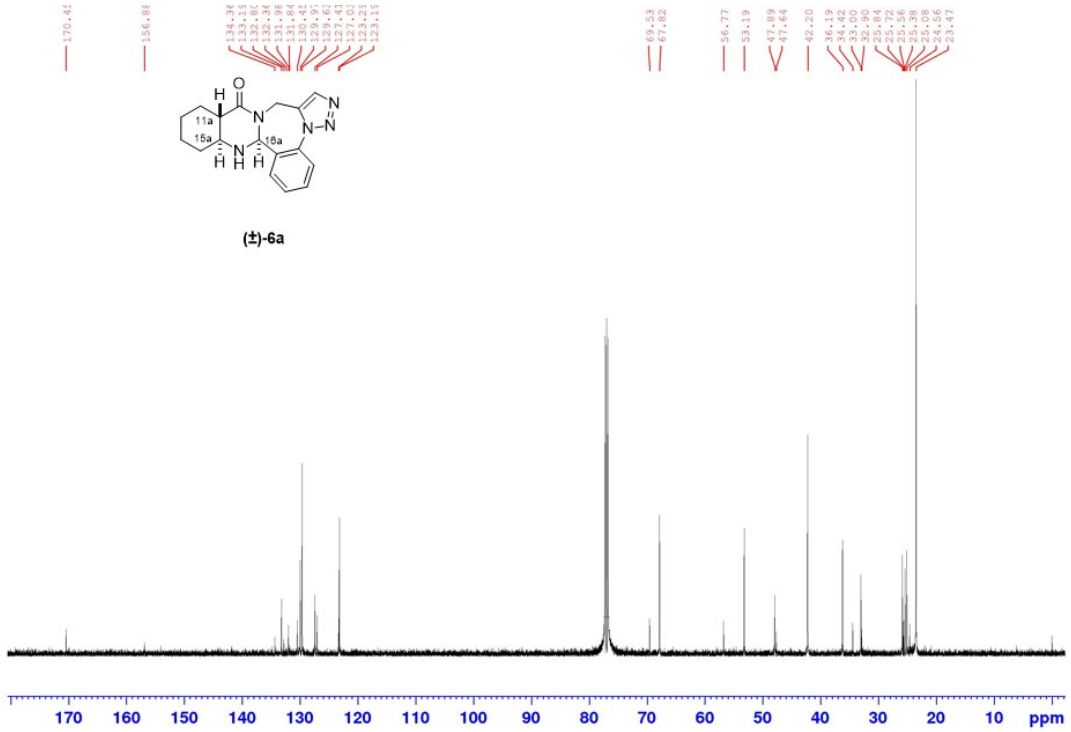

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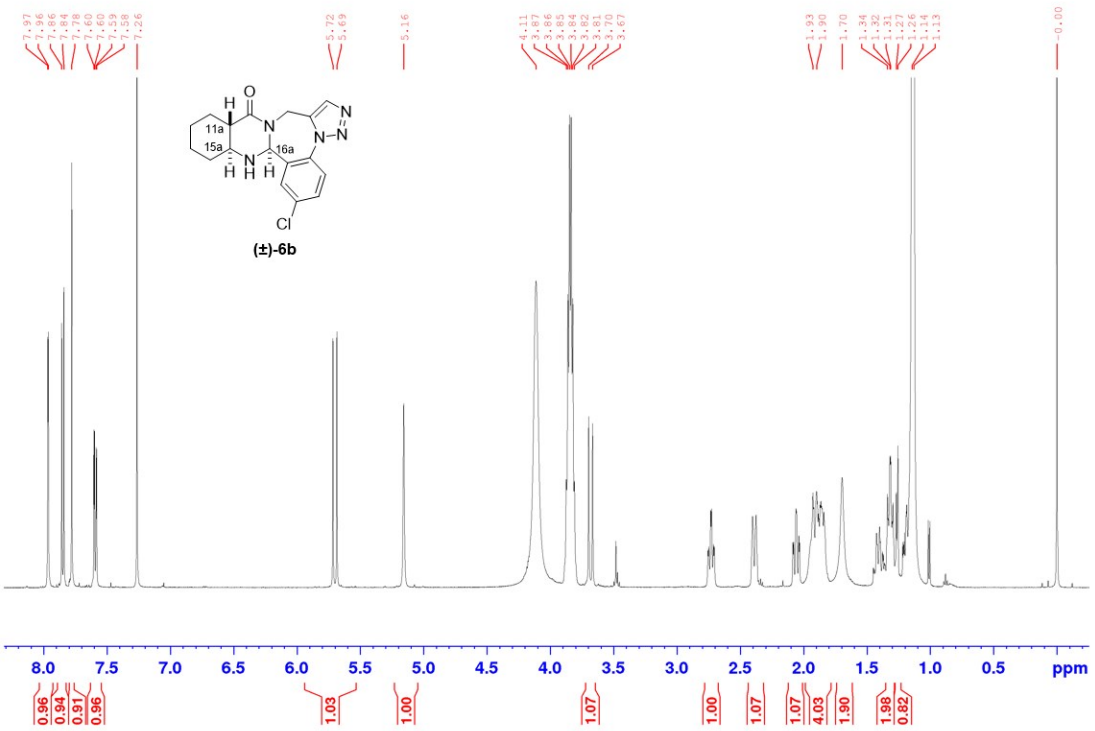

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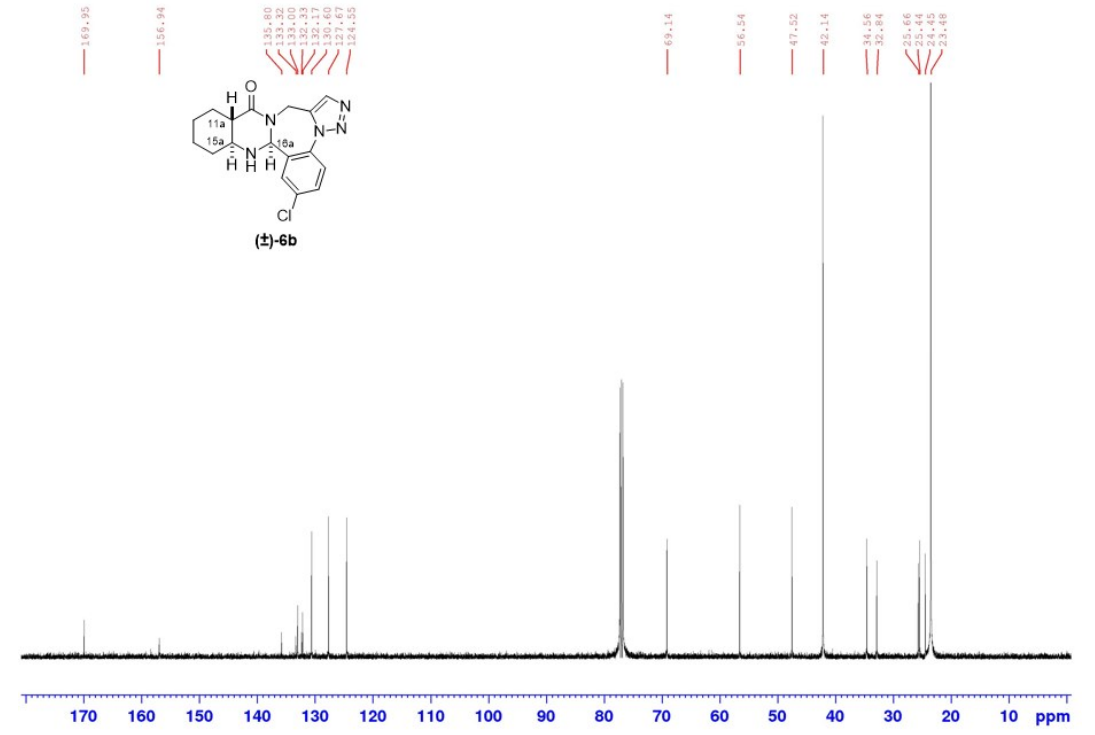

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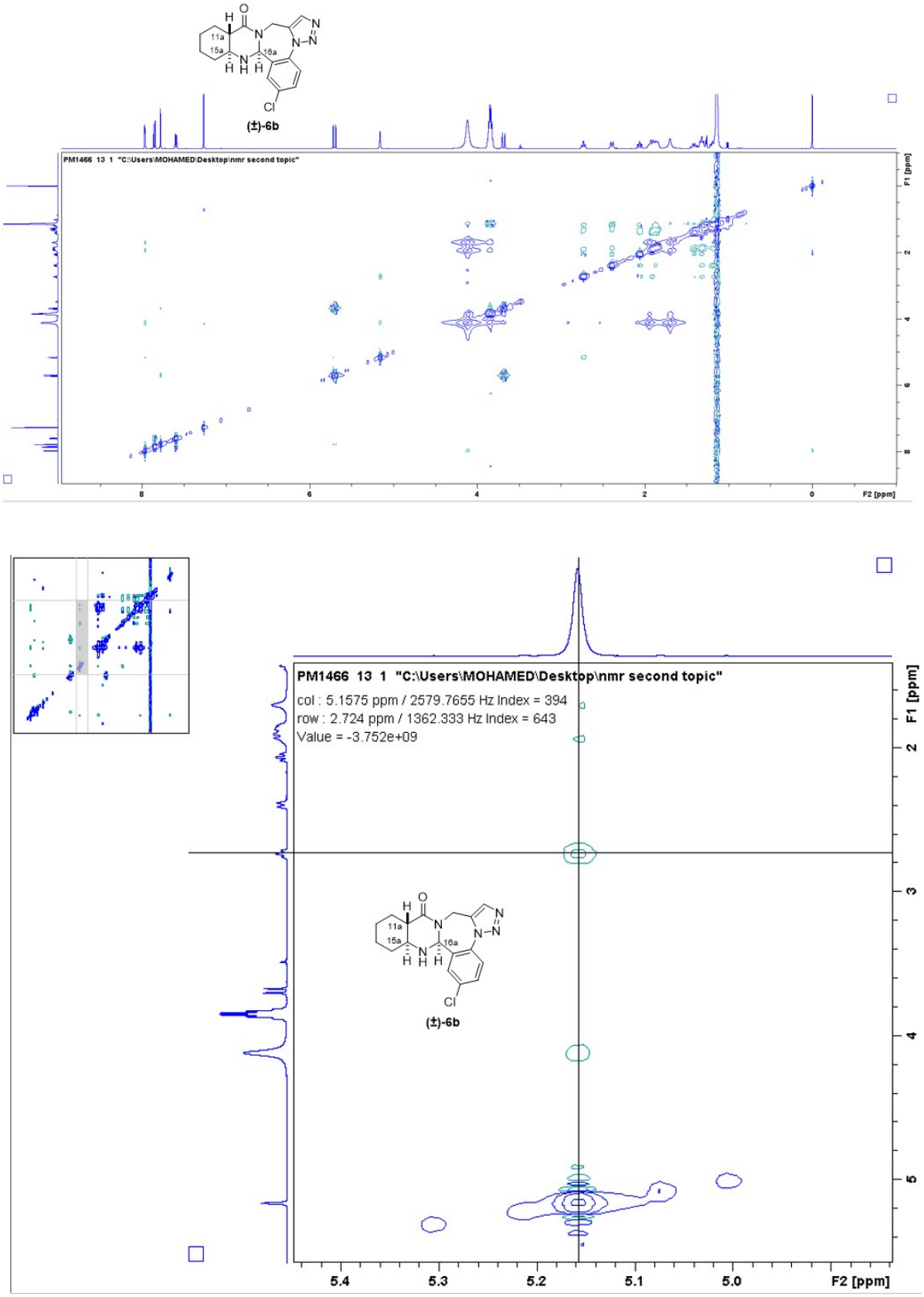
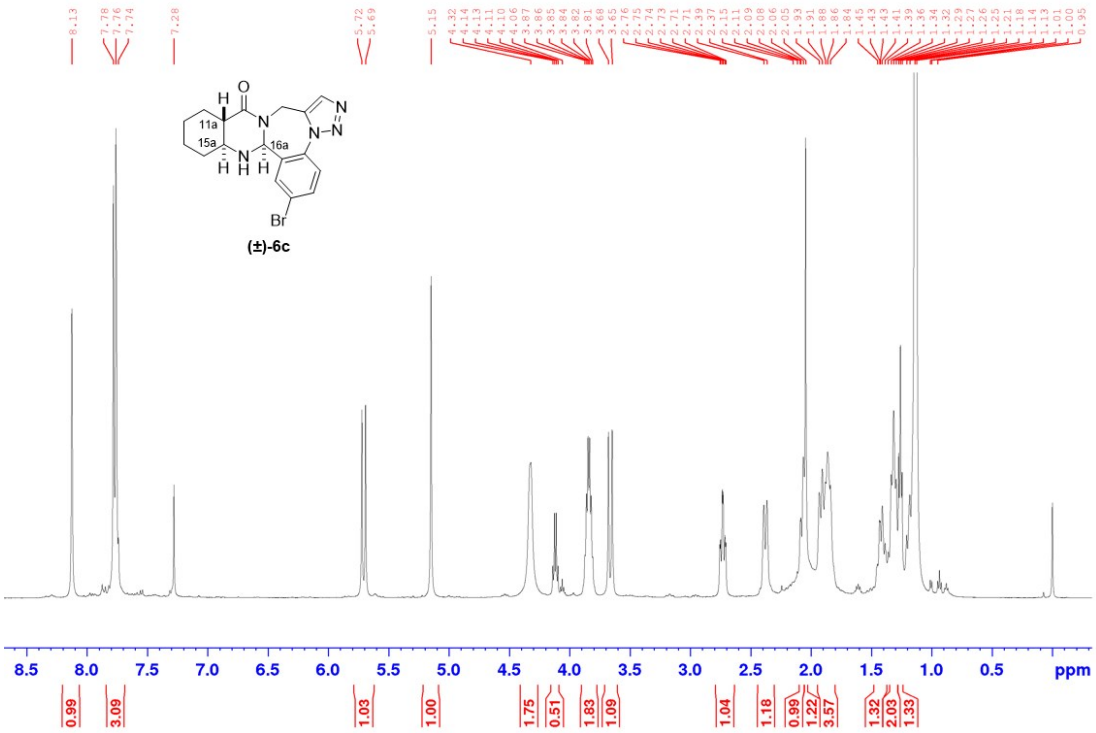


NOESY NMR Spectrum of (*r*-11a,*t*-15a,*t*-16a)-2-chloro-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-6b** ($CDCl_3$)



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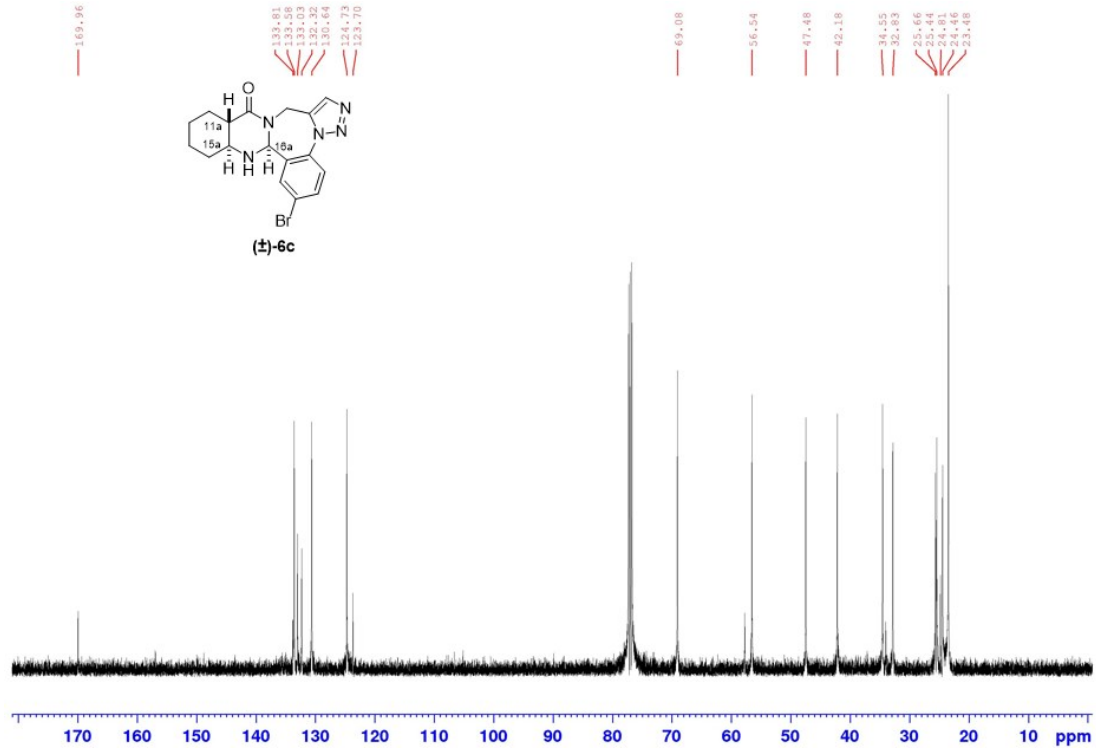

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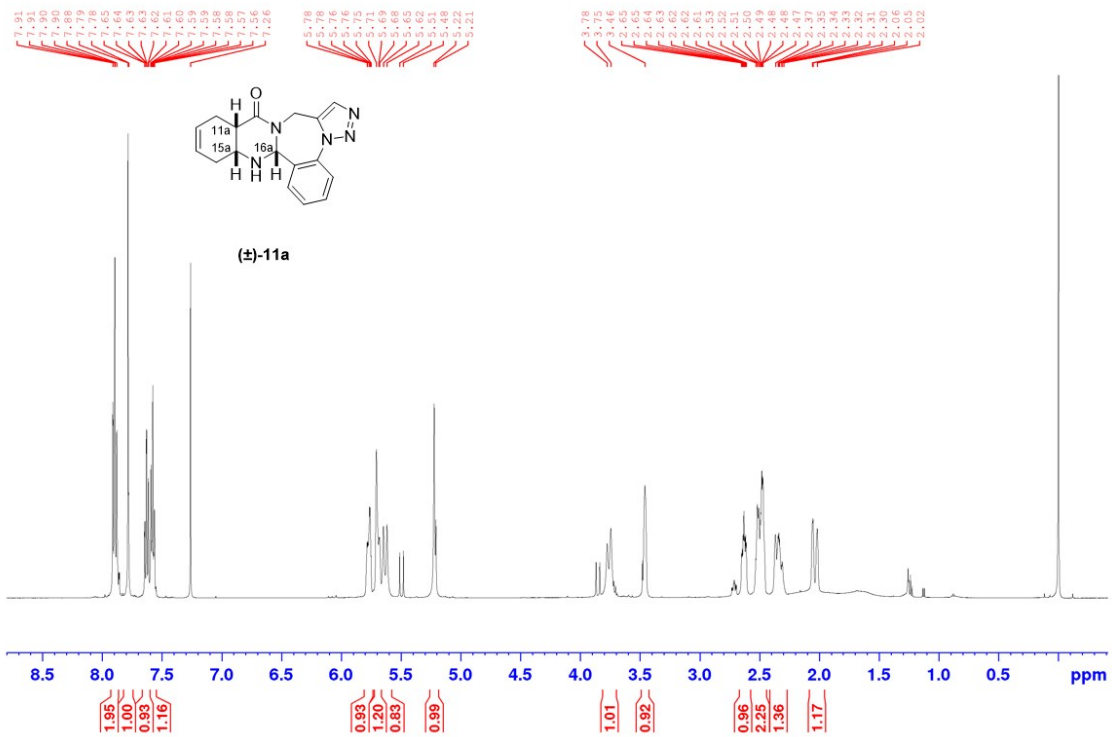

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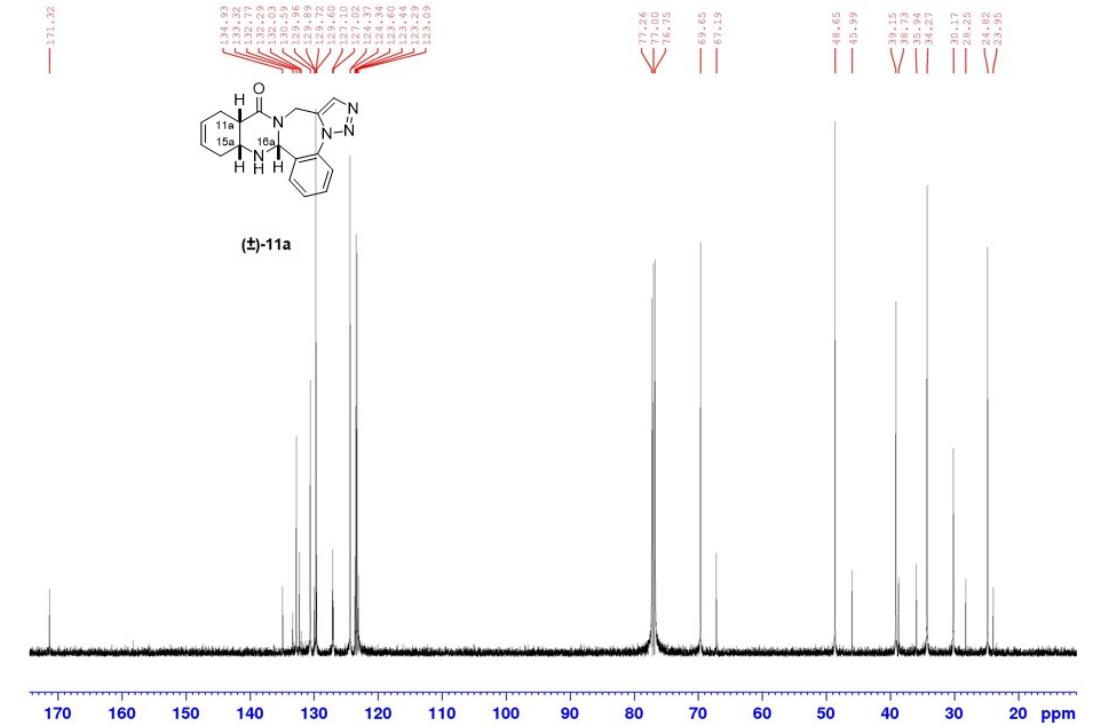

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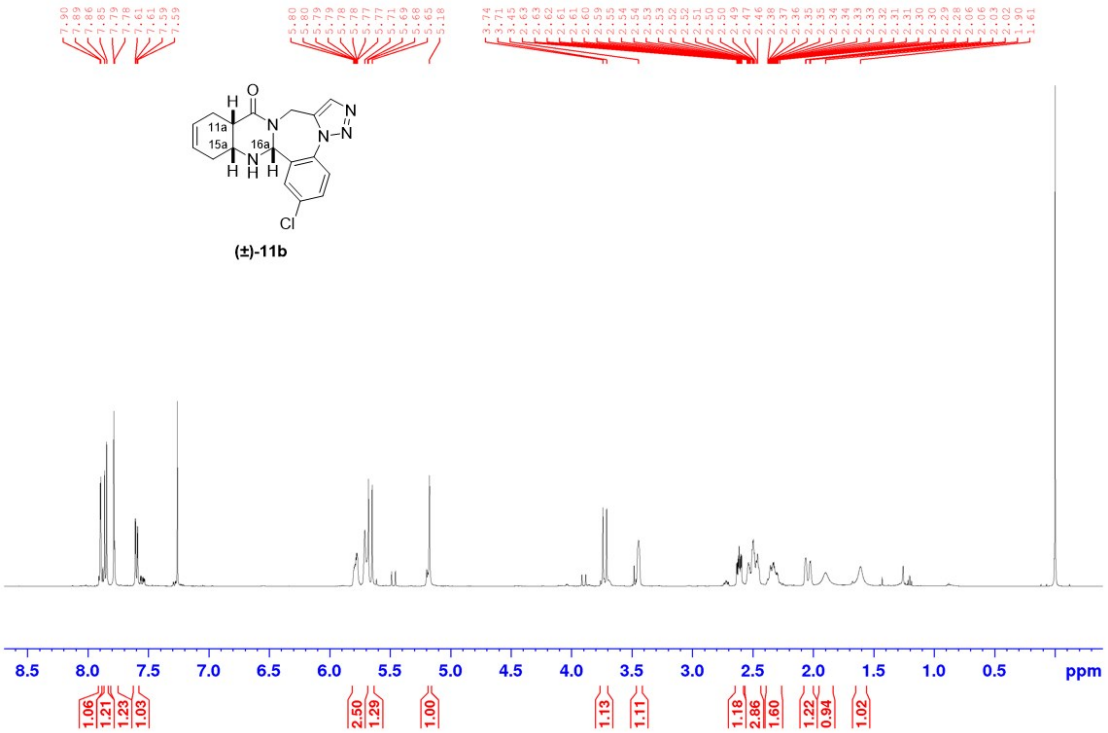
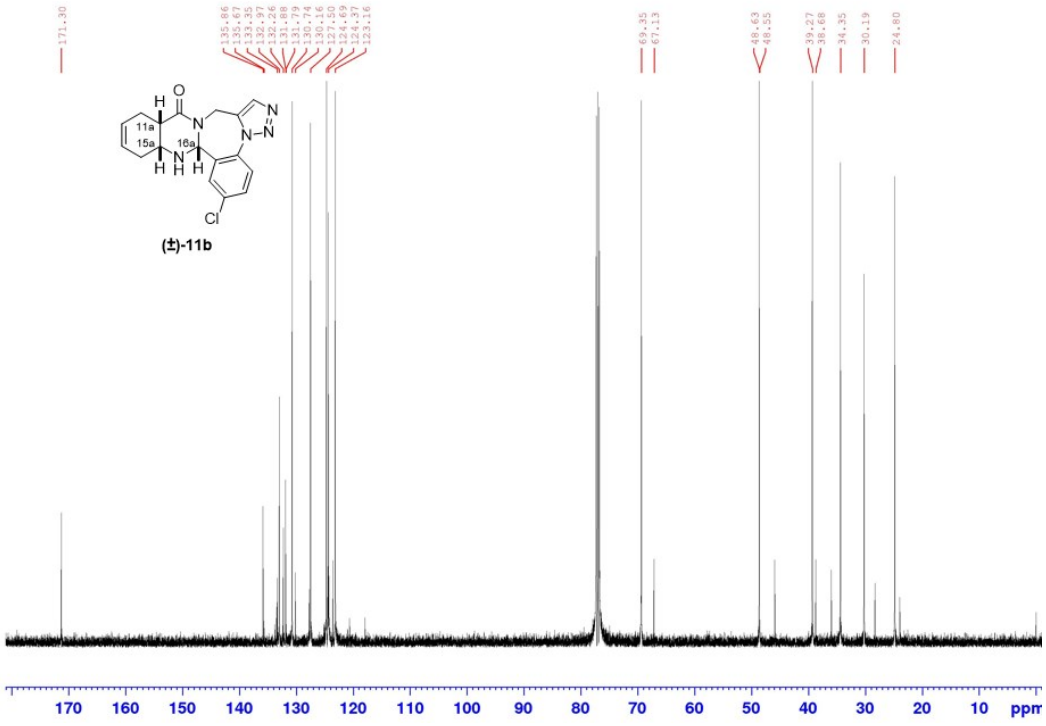
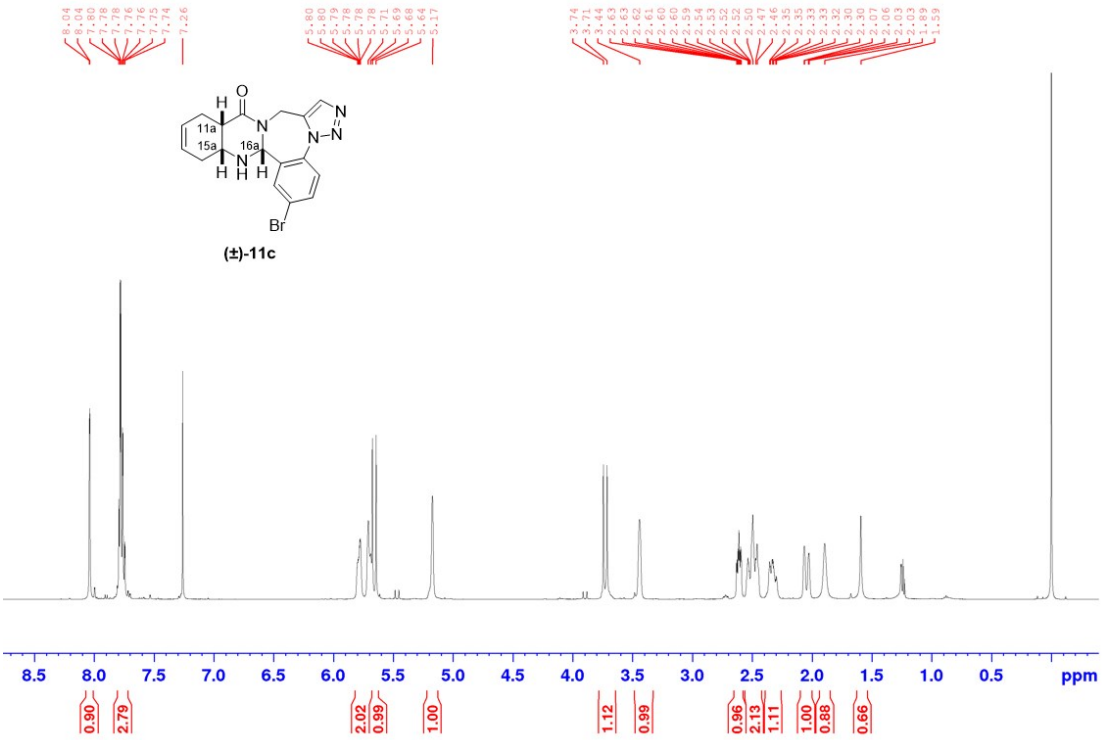


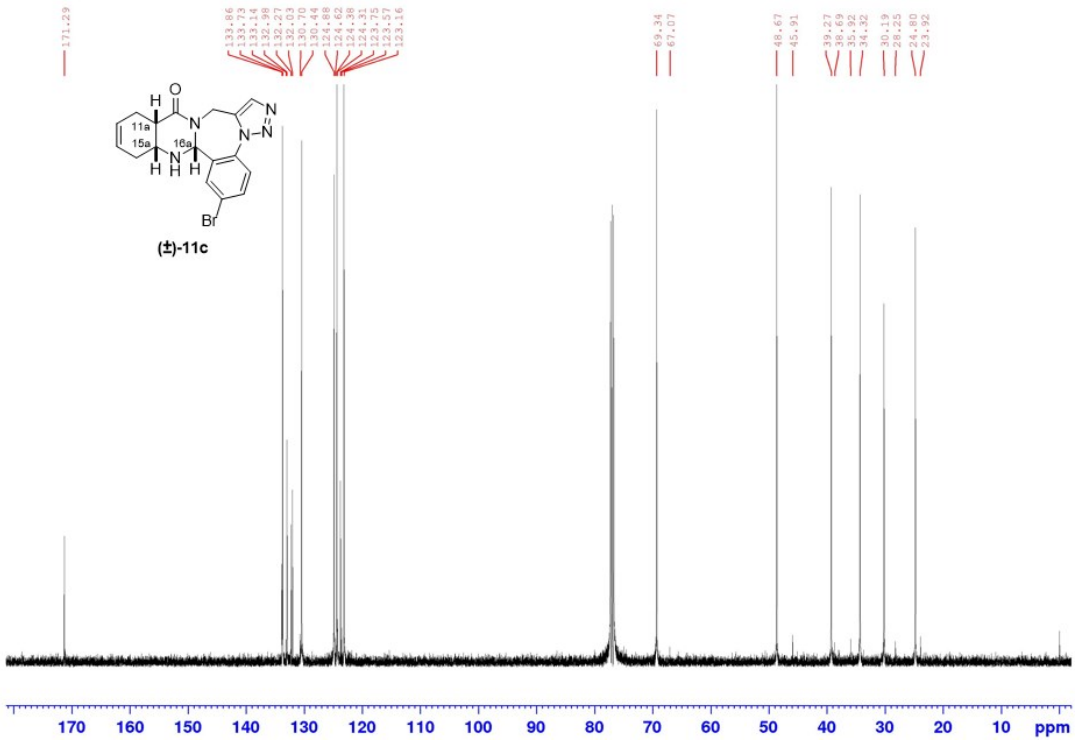
^{1}H NMR Spectrum of (*r*-11a,*c*-15a,*c*-16a)-2-chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-11b** ($CDCl_3$)



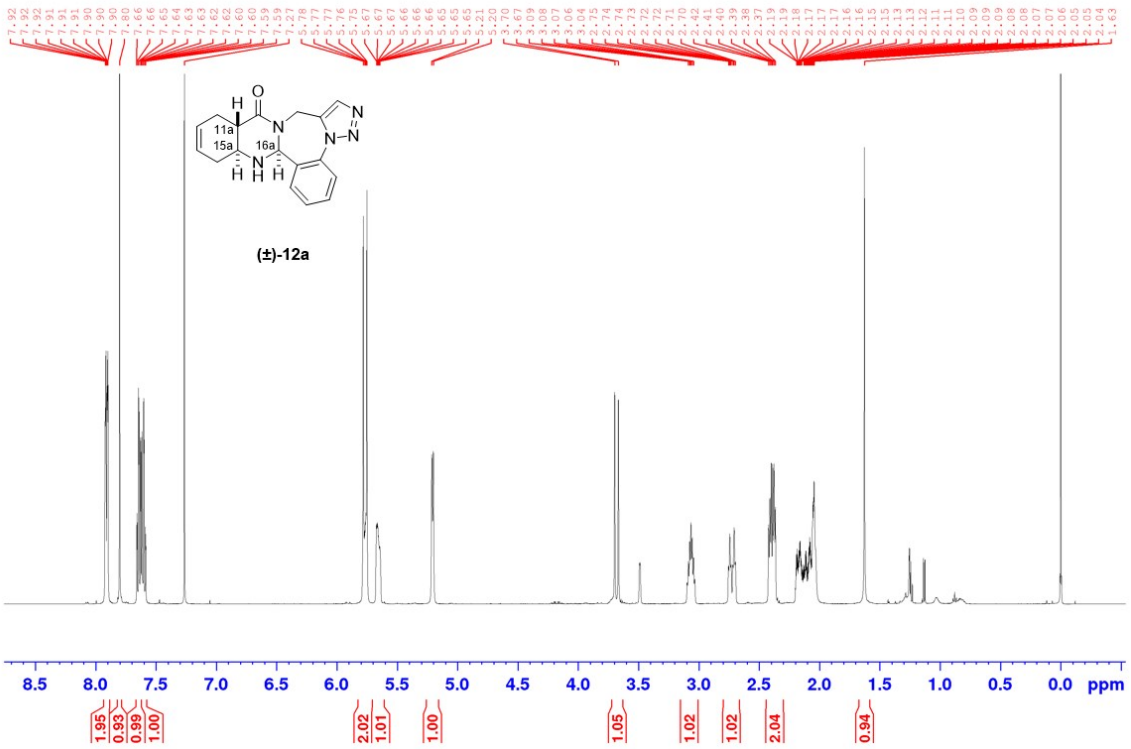
^{13}C NMR Spectrum (*r*-11a,*c*-15a,*c*-16a)-2-chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-11b** ($CDCl_3$)



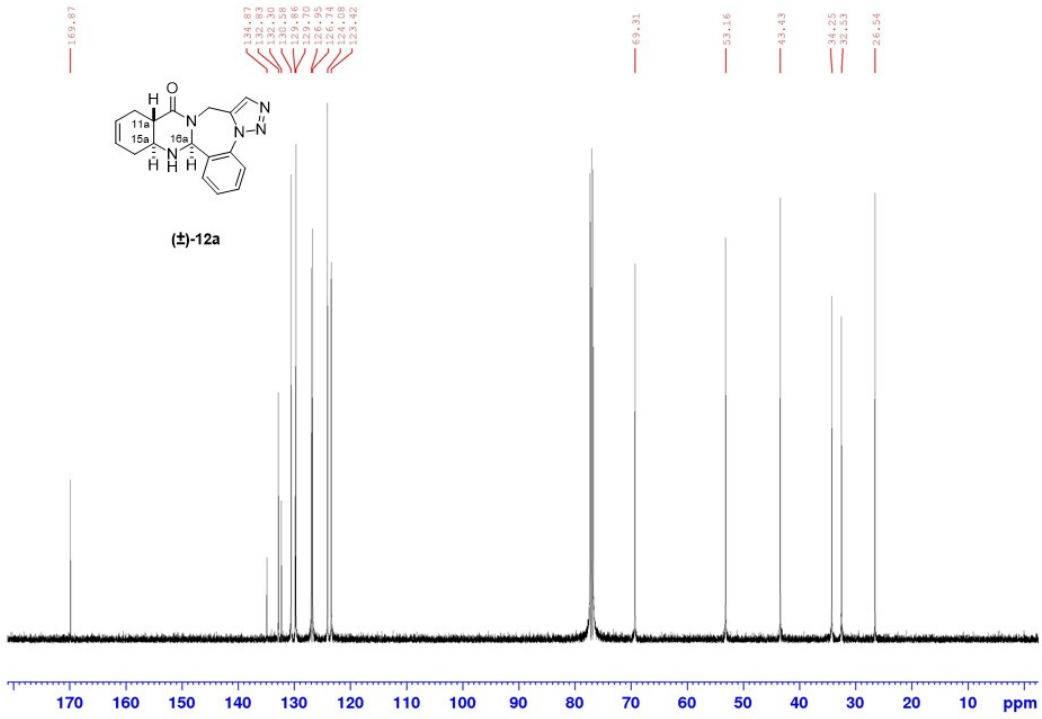
^{1}H NMR Spectrum of (*r*-11a,*c*-15a,*c*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-11c** ($CDCl_3$)



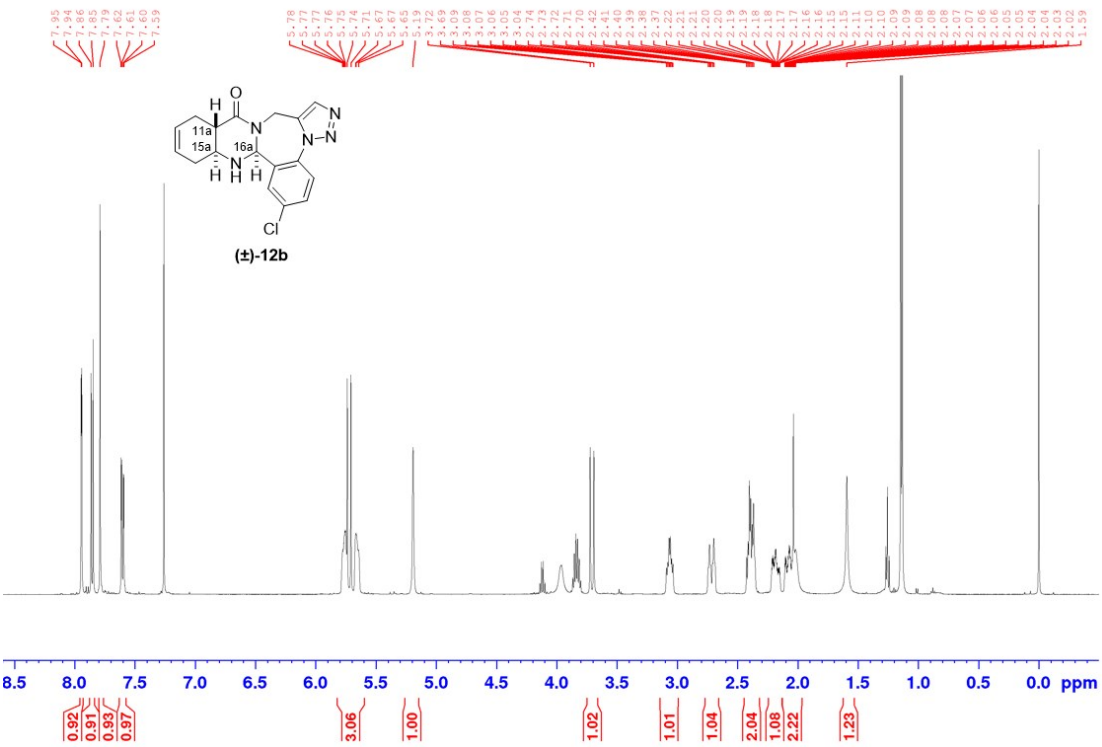
^{13}C NMR Spectrum of (*r*-11a,*c*-15a,*c*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-11c** ($CDCl_3$)



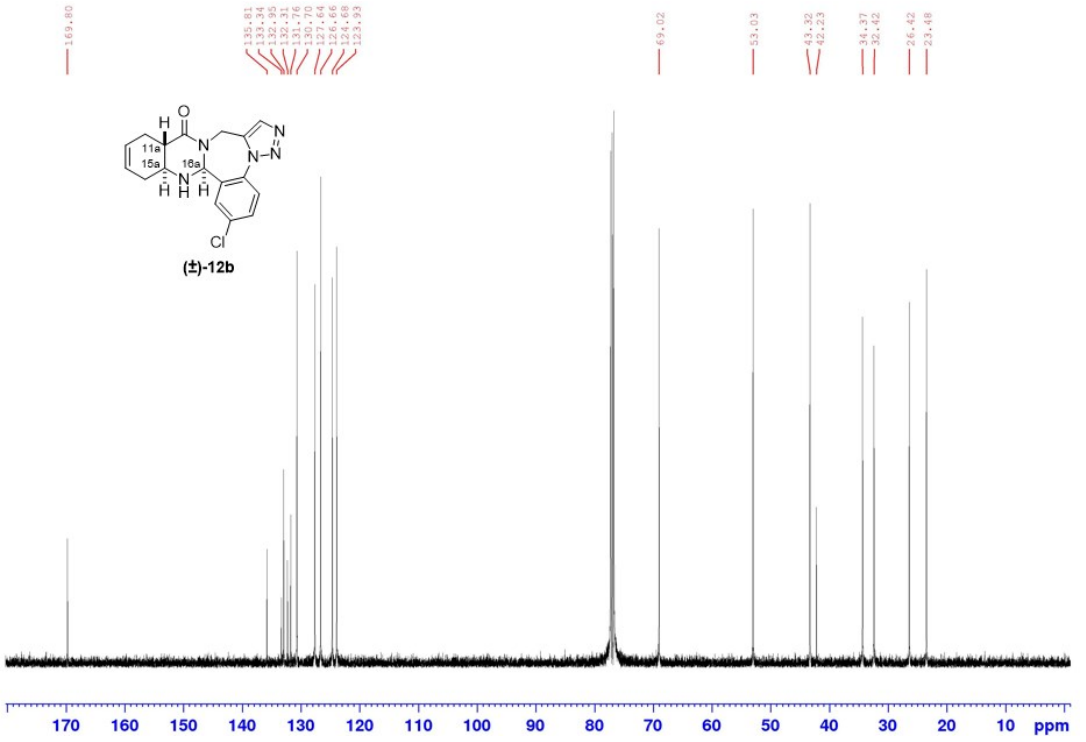
^{1}H NMR Spectrum of (*r*-11a,*t*-15a,*t*-16a)-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-12a** ($CDCl_3$)



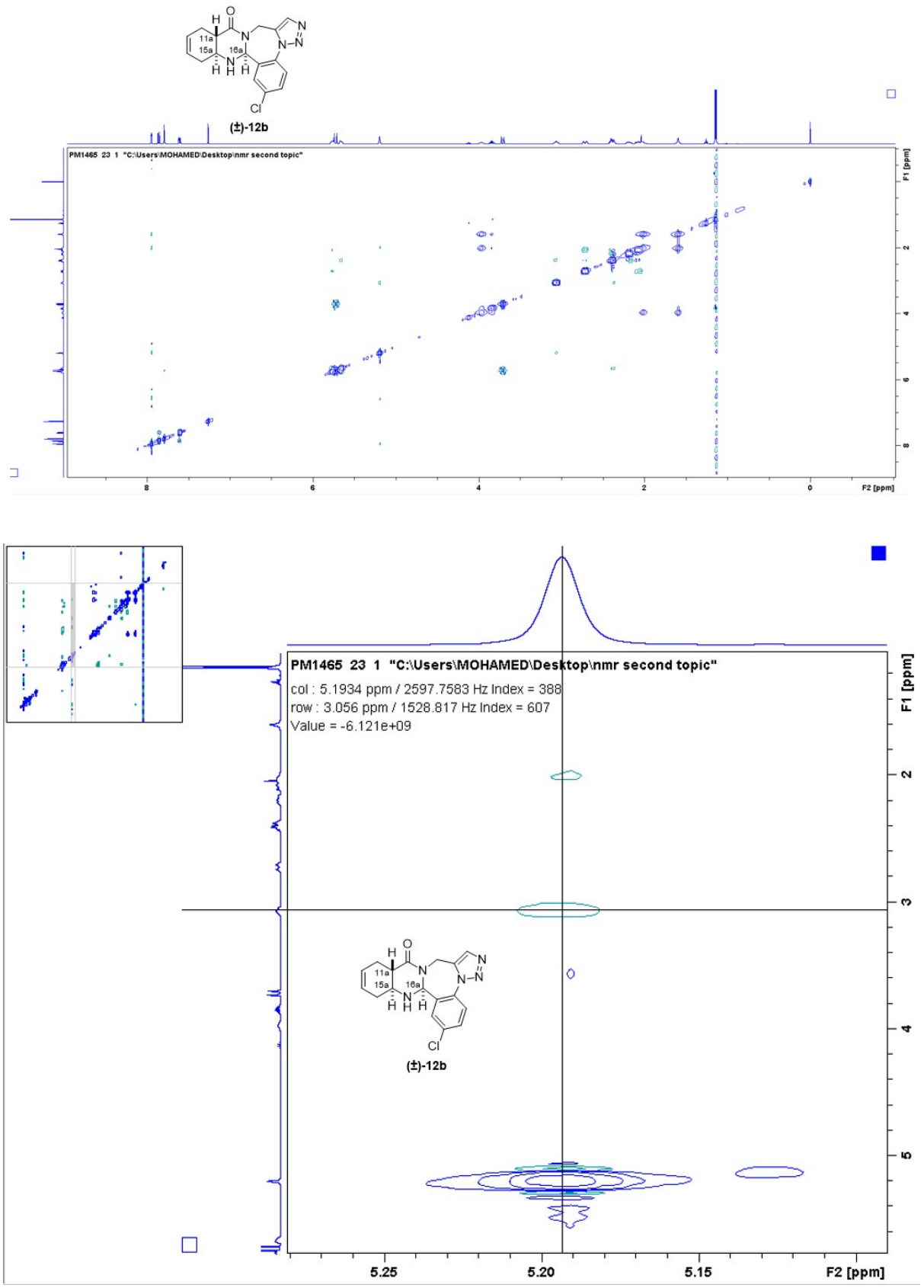
^{13}C NMR Spectrum of (*r*-11a,*t*-15a,*t*-16a)-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-12a** ($CDCl_3$)



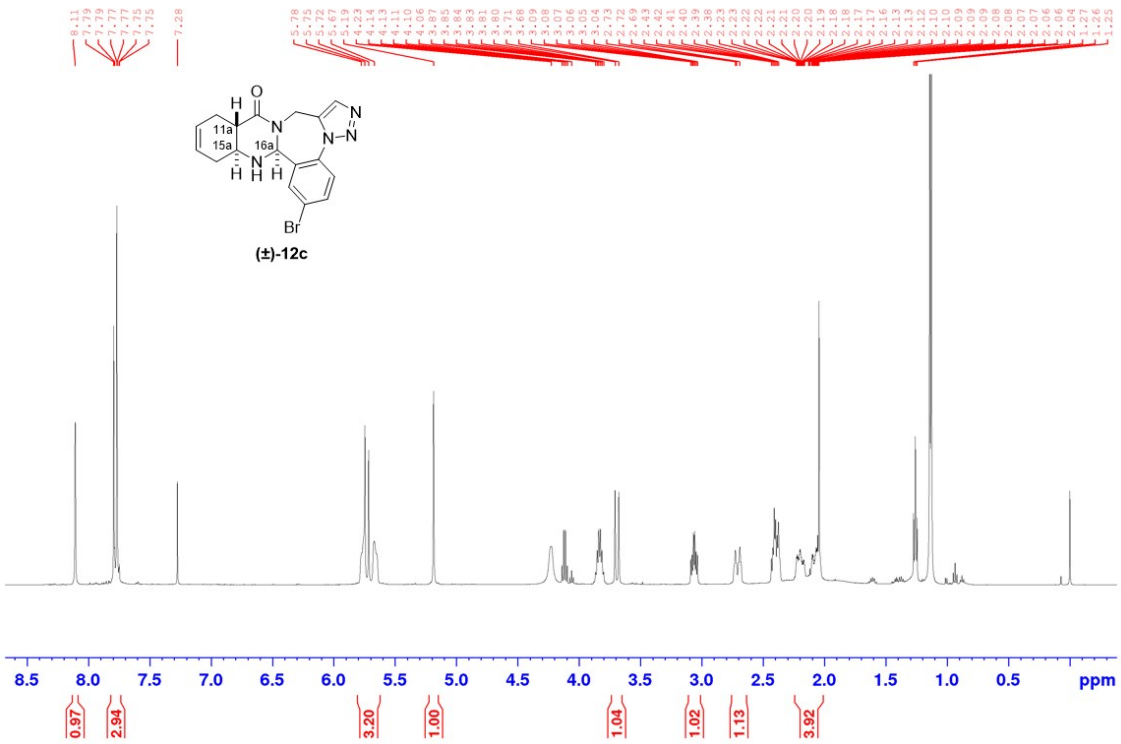
^{1}H NMR Spectrum of (*r*-11a,*t*-15a,*t*-16a)-2-chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-12b** ($CDCl_3$)



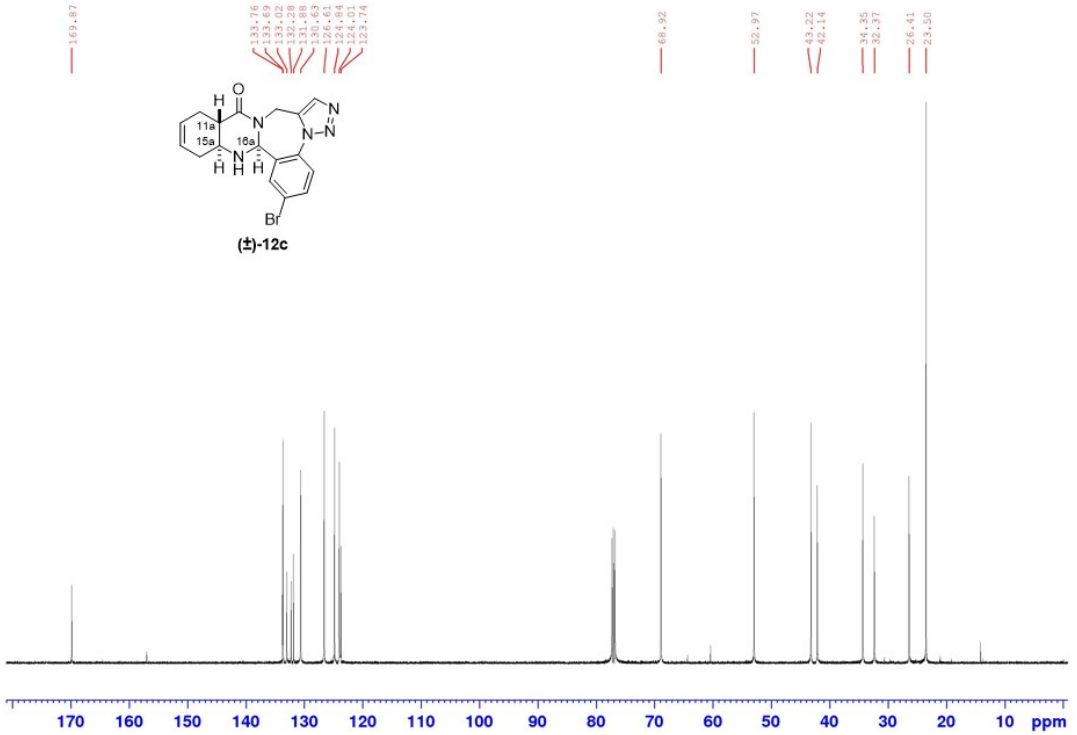
^{13}C NMR Spectrum of (*r*-11a,*t*-15a,*t*-16a)-2-chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-12b** ($CDCl_3$)



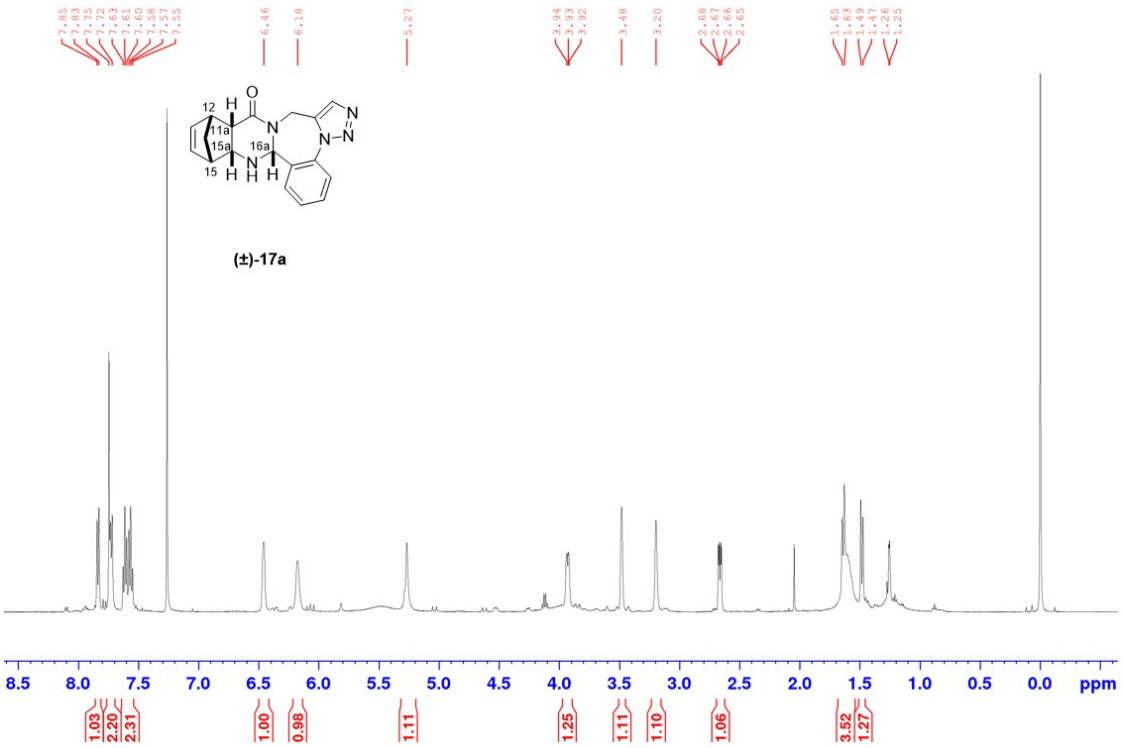
NOESY NMR Spectrum of (*r*-11a,*t*-15a,*t*-16a)-2-chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-12b** ($CDCl_3$)



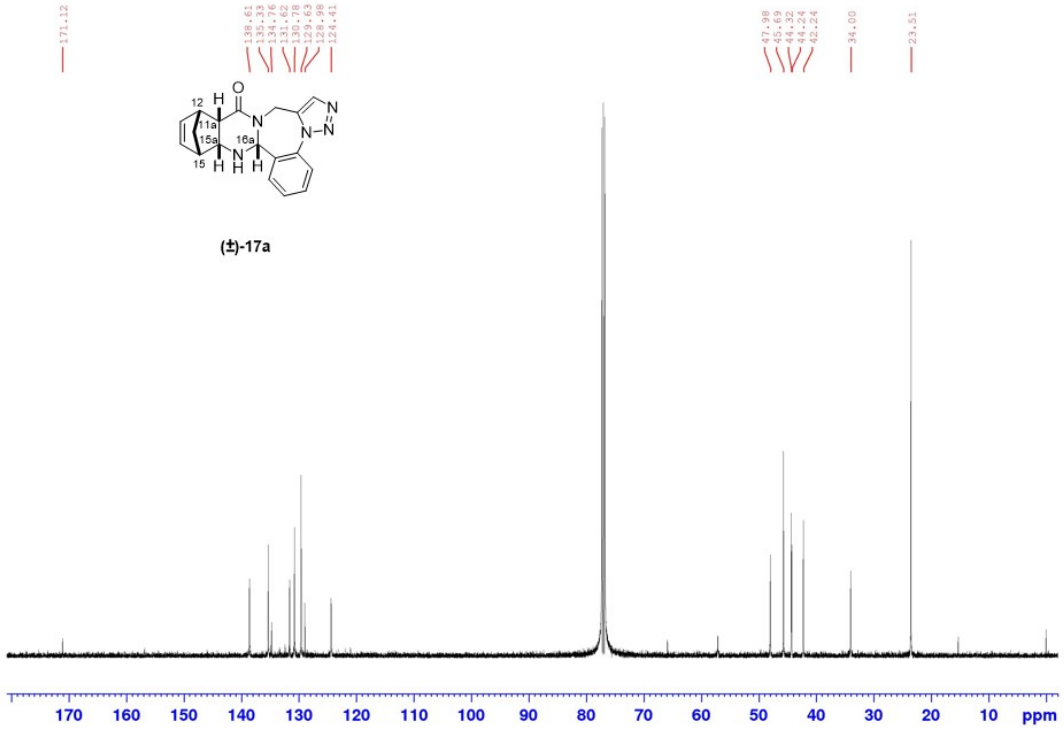
^{1}H NMR Spectrum of (*r*-11a,*t*-15a,*t*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-12c** ($CDCl_3$)



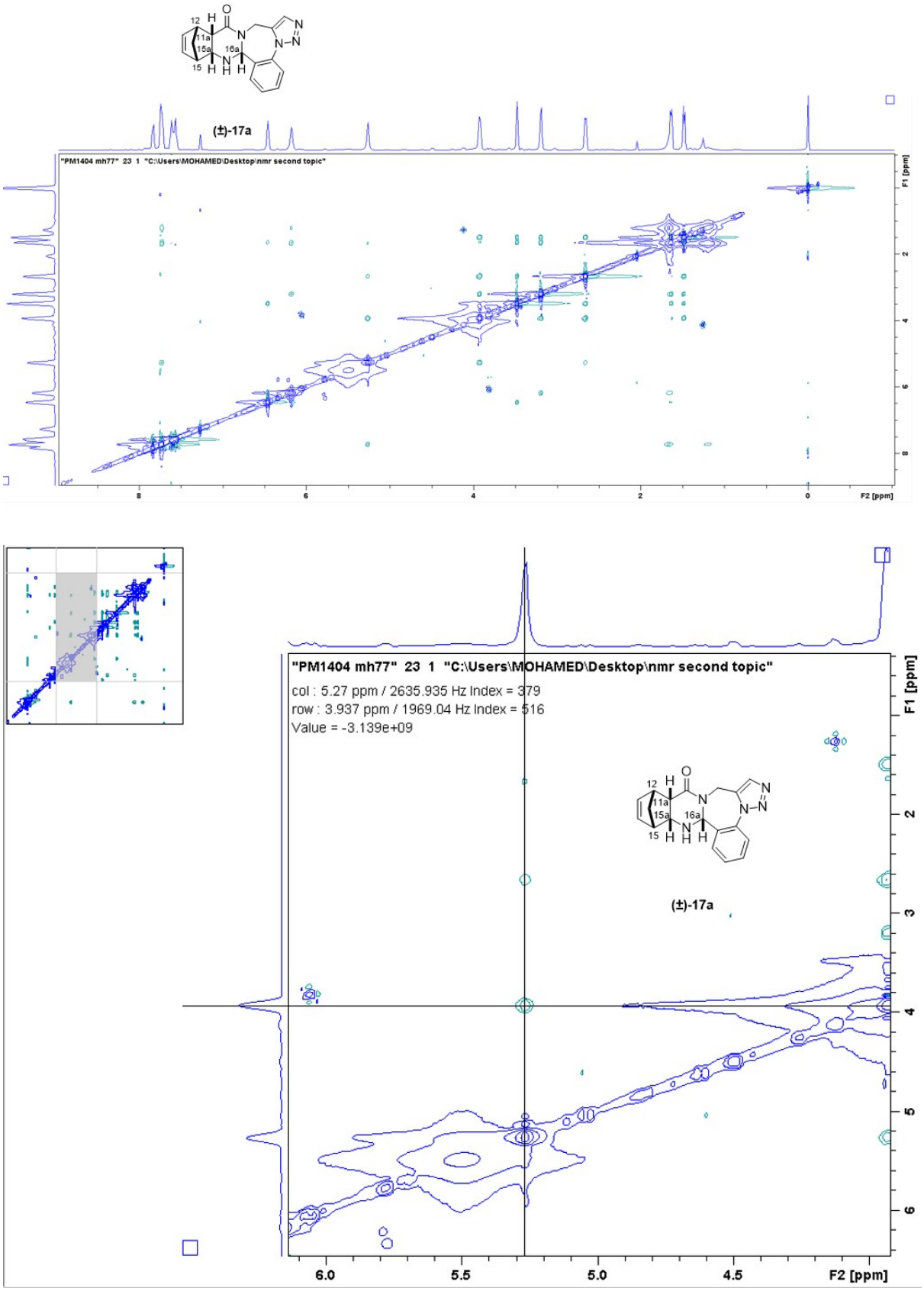
^{13}C NMR Spectrum of (*r*-11a,*t*-15a,*t*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-12c** ($CDCl_3$)



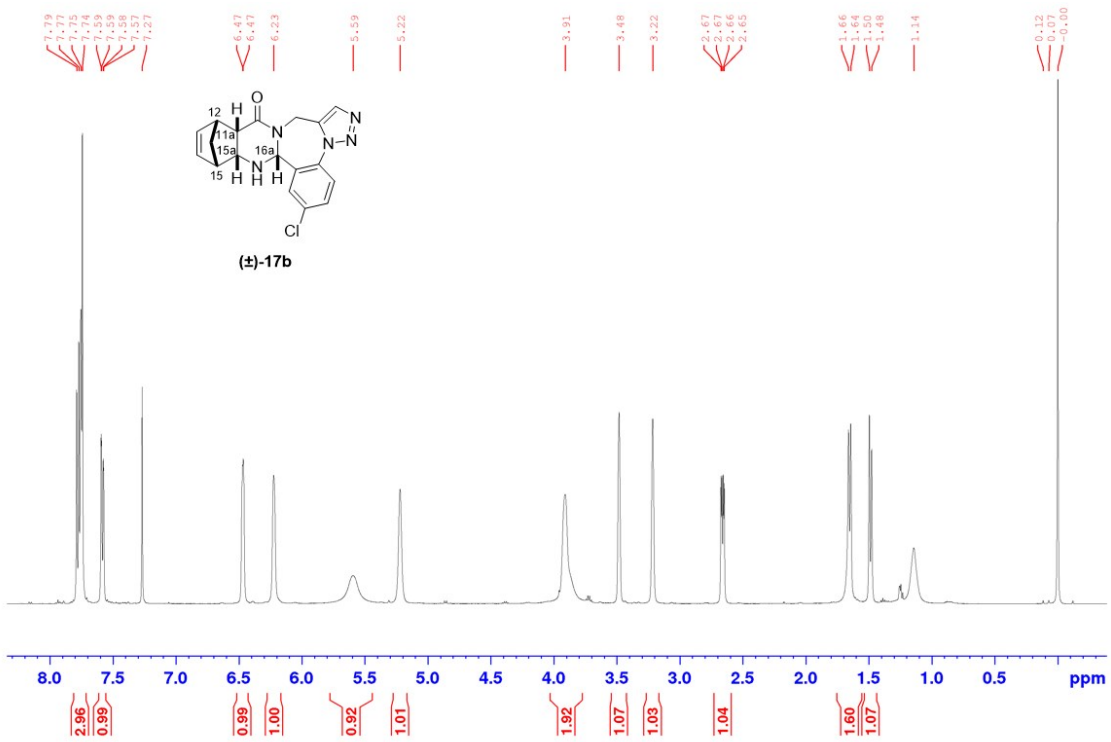
^{1}H NMR Spectrum of (*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-17a** ($CDCl_3$)



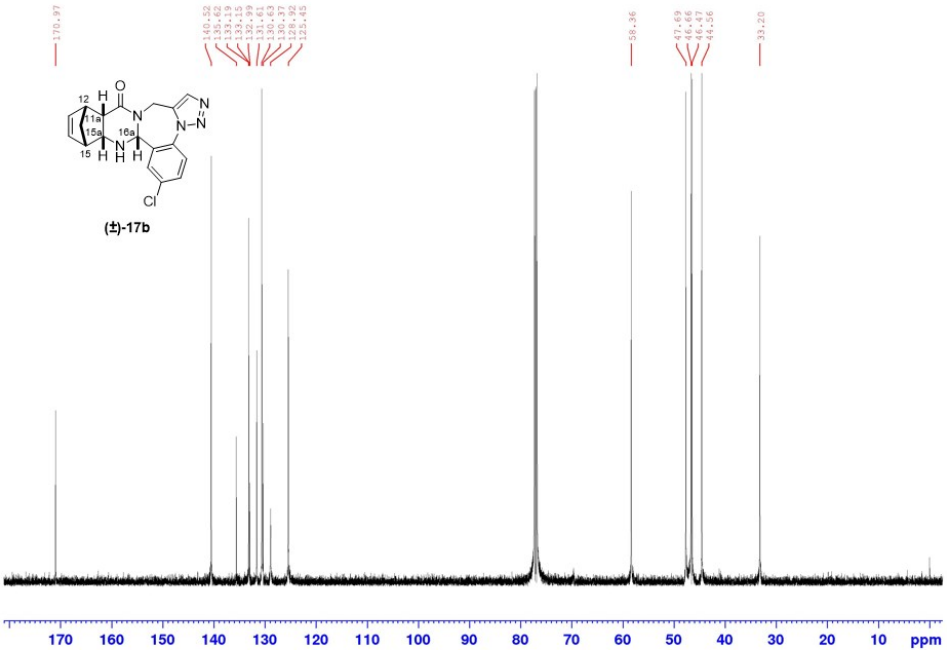
^{13}C NMR Spectrum of (*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-17a** ($CDCl_3$)



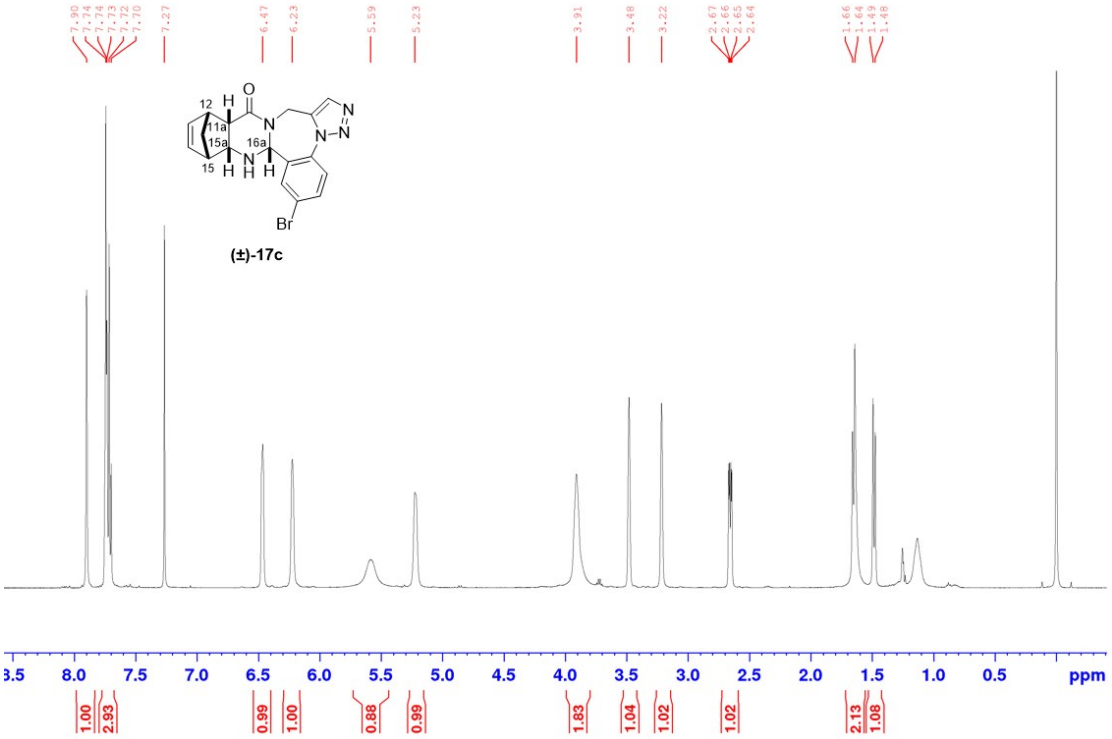
NOESY NMR Spectrum of (*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-17a** ($CDCl_3$)



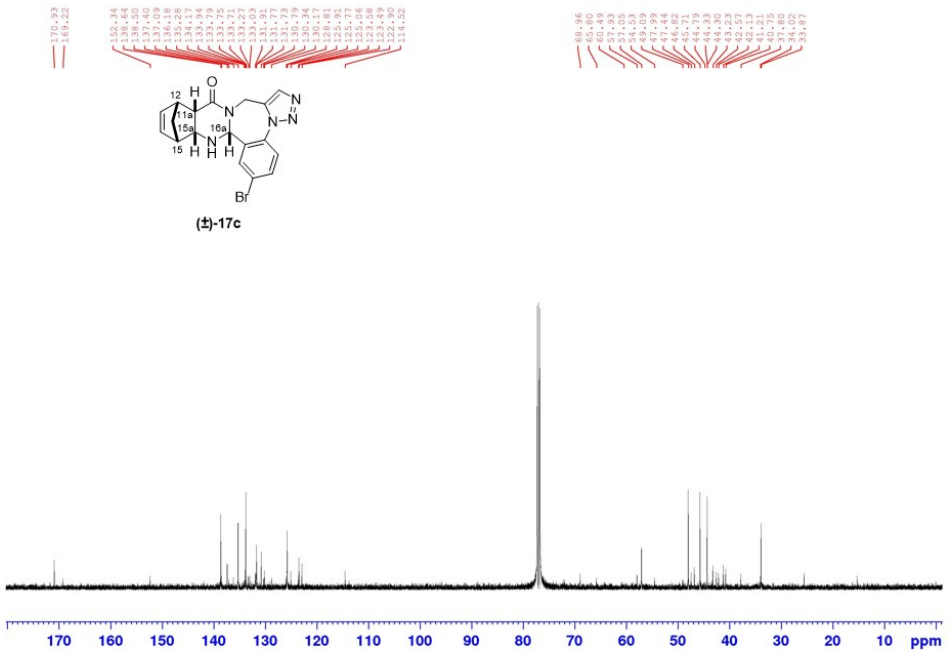
^{1}H NMR Spectrum of (*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-chloro-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-17b** ($CDCl_3$)



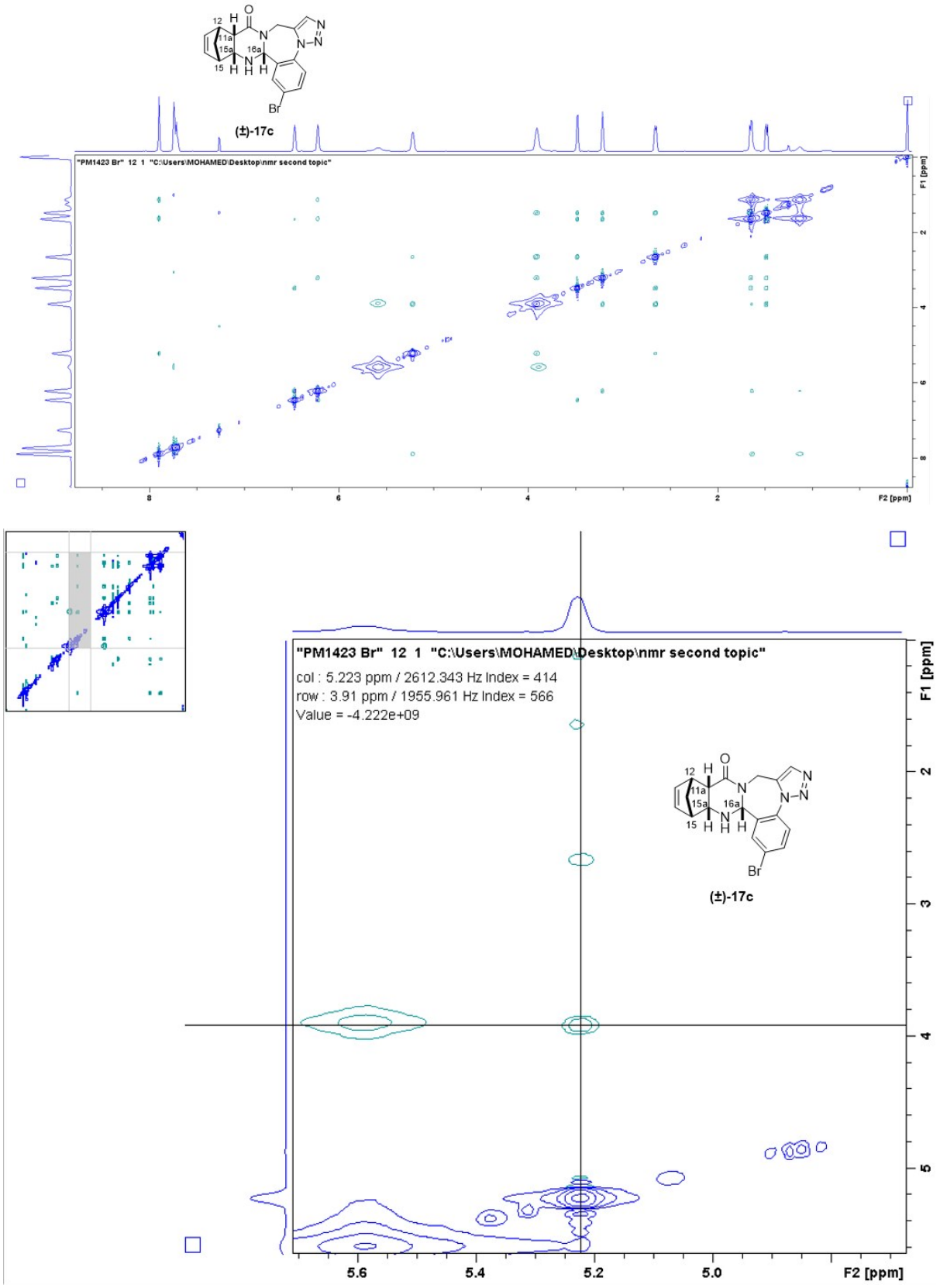
^{13}C NMR Spectrum of (*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-chloro-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-17b** ($CDCl_3$)



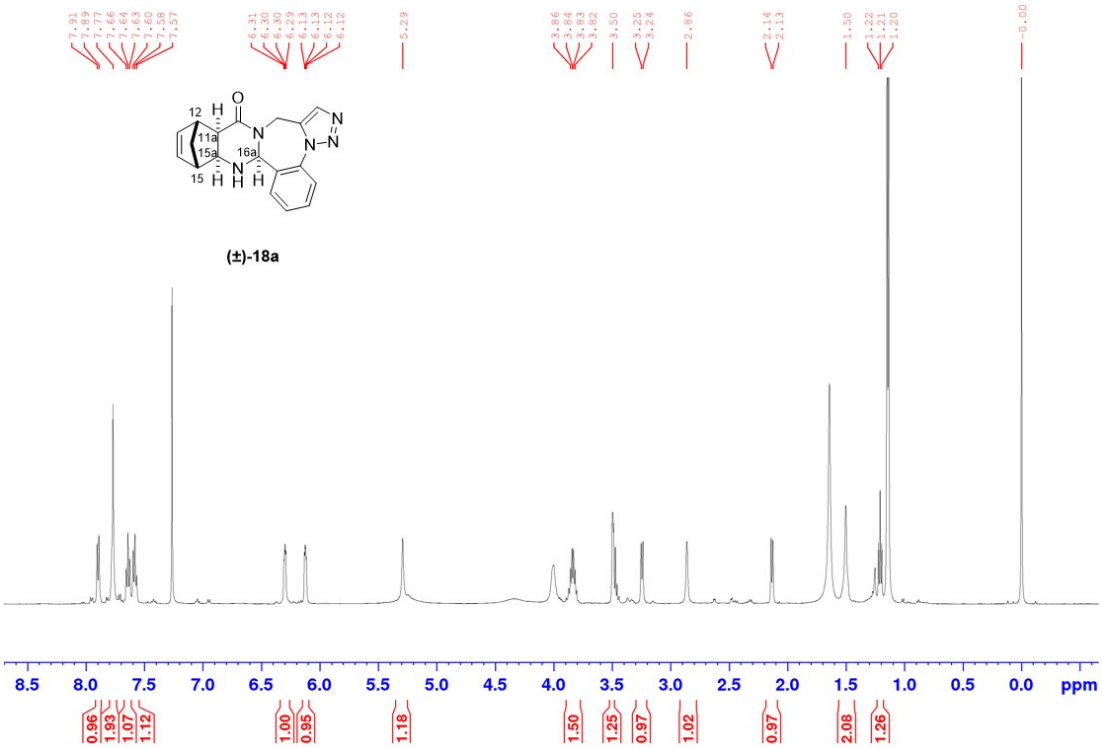
^{1}H NMR Spectrum of (*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-17c** ($CDCl_3$)



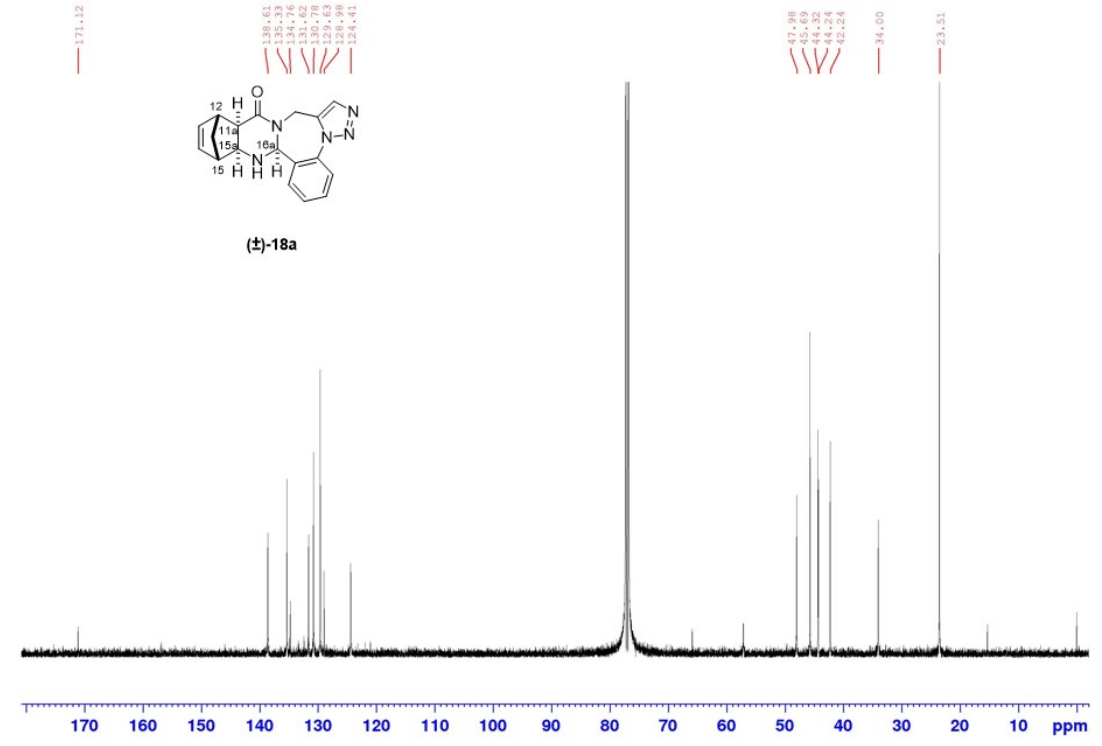
^{13}C NMR Spectrum of (*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-17c** ($CDCl_3$)



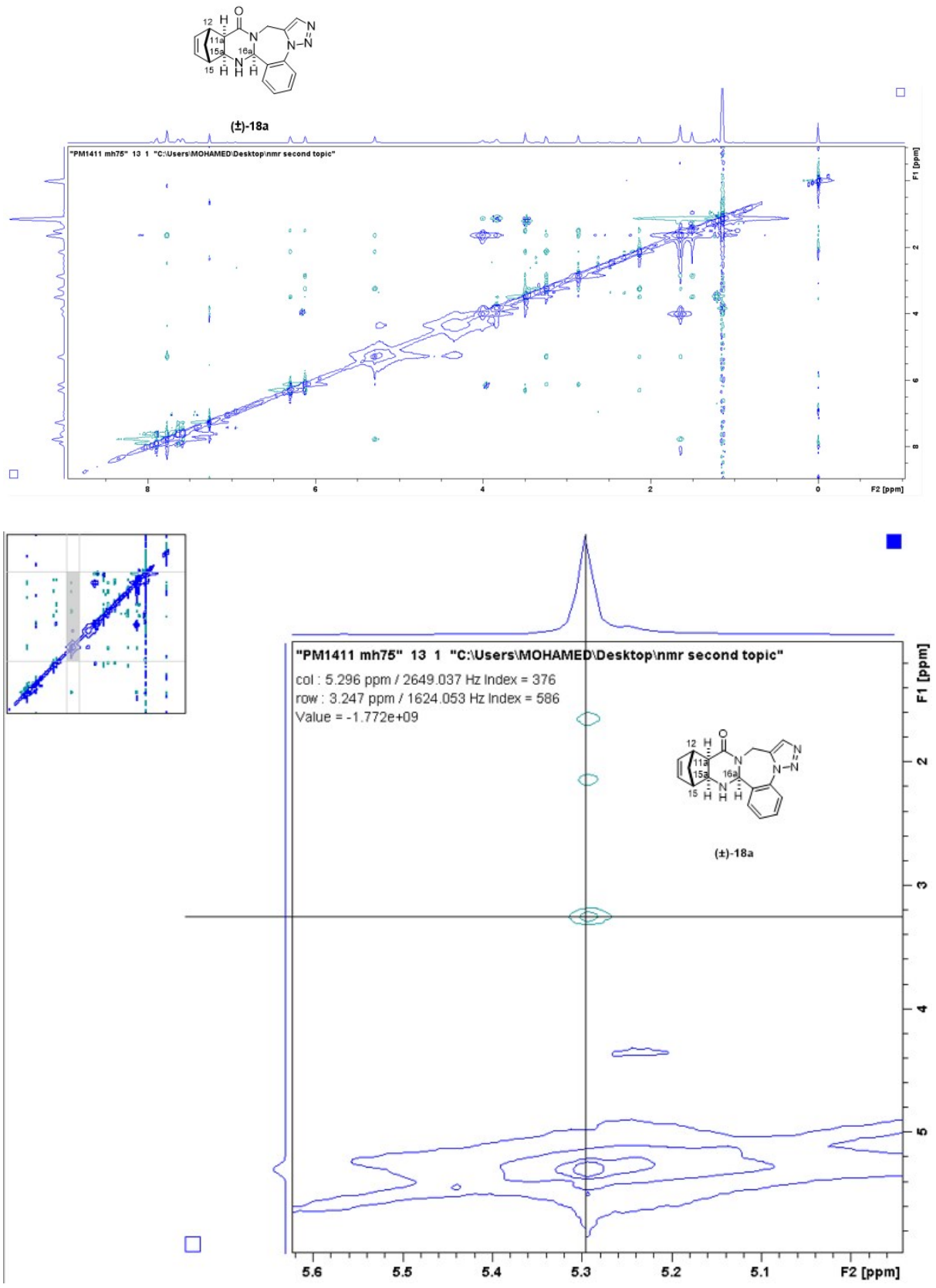
NOESY NMR Spectrum of (*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-17c** ($CDCl_3$)



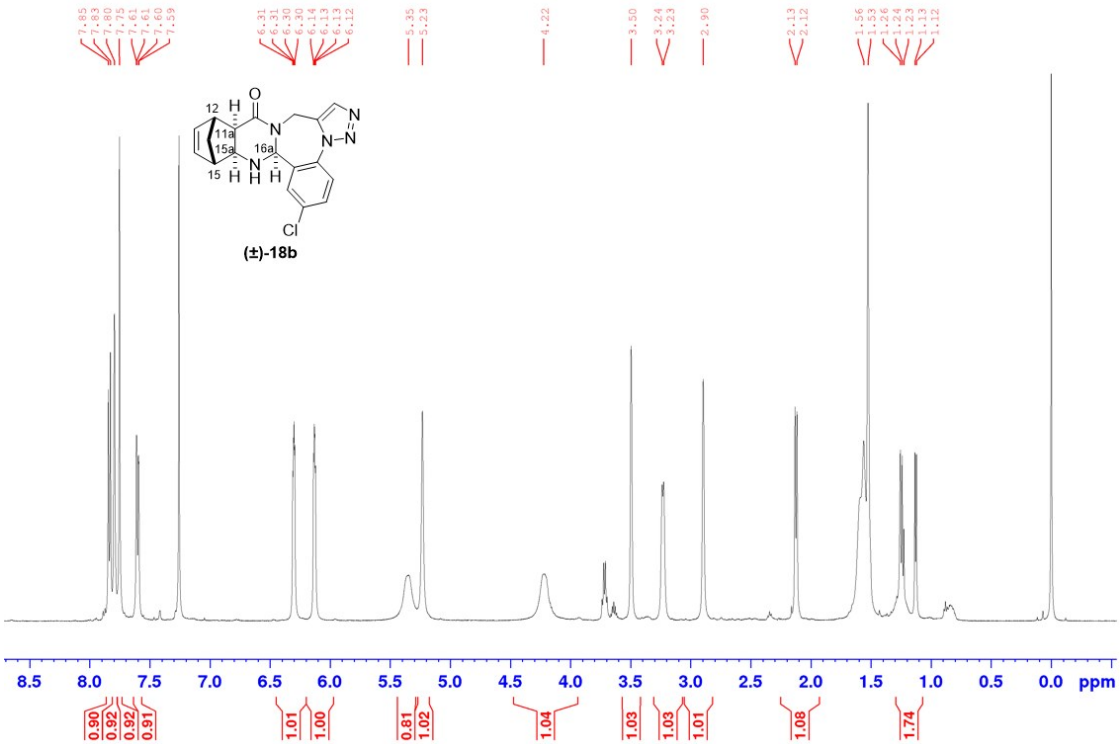
^{1}H NMR Spectrum of (*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-hexahydro-12,15 methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]-quinazolin-11(9*H*)-one **18a** ($CDCl_3$)



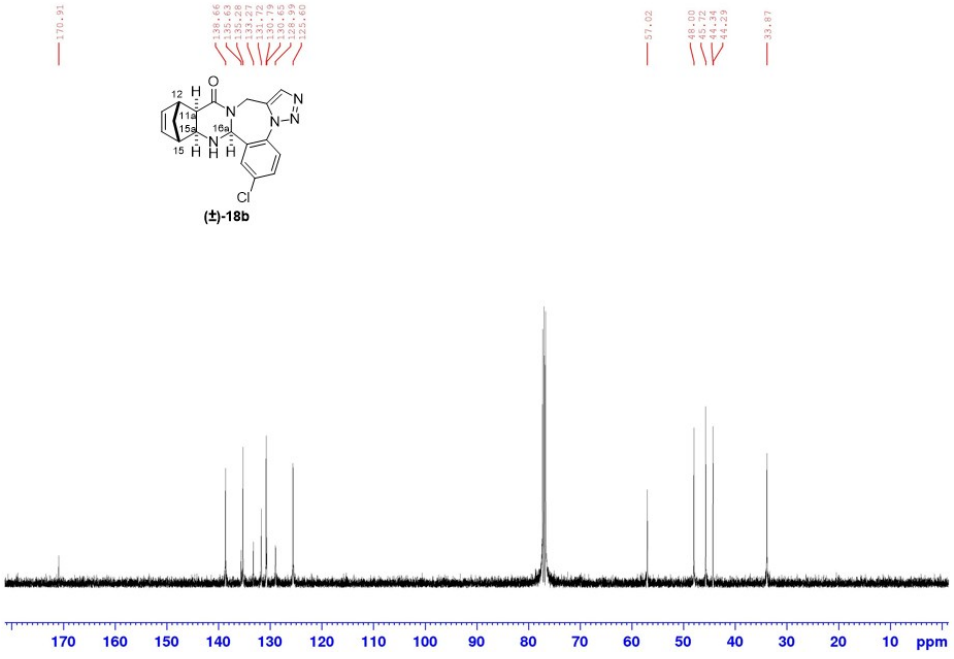
^{13}C NMR Spectrum of (*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-hexahydro-12,15 methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]-quinazolin-11(9*H*)-one **18a** ($CDCl_3$)



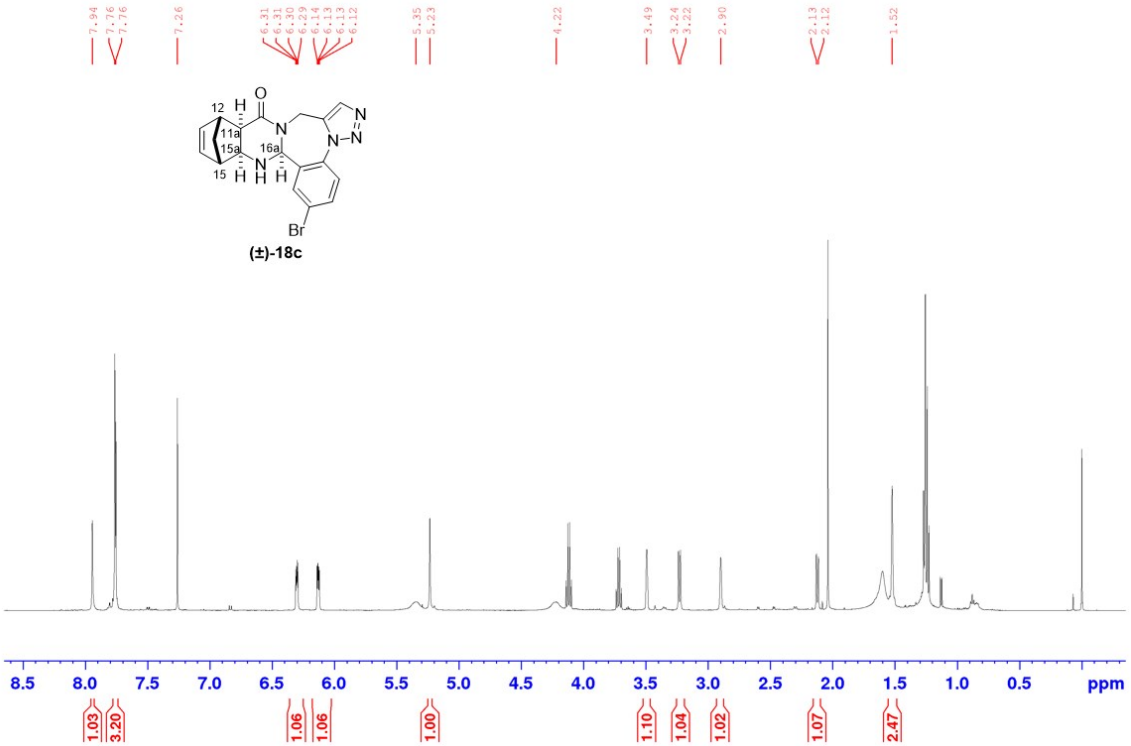
NOESY NMR Spectrum of (*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-hexahydro-12,15 methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]-quinazolin-11(9*H*)-one **18a** ($CDCl_3$)



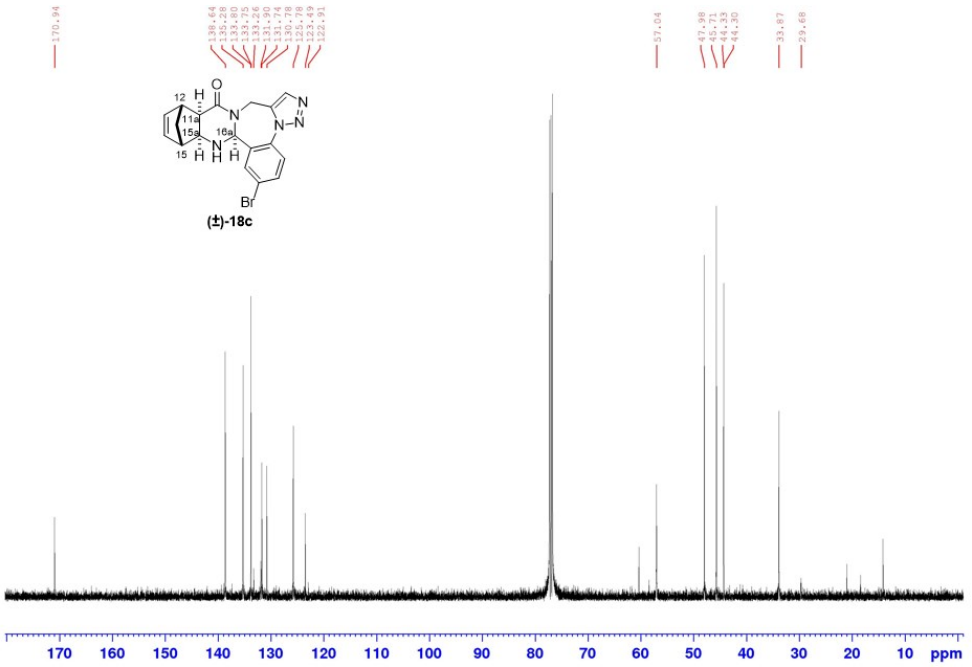
^{1}H NMR Spectrum of (*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-2-chloro-11a,12,15,15a,16,16a-hexa-hydro-12,15-methanobenzo[5,6][1,2,3]triazolo-[5',1':3,4][1,4]-diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-18b** ($CDCl_3$)



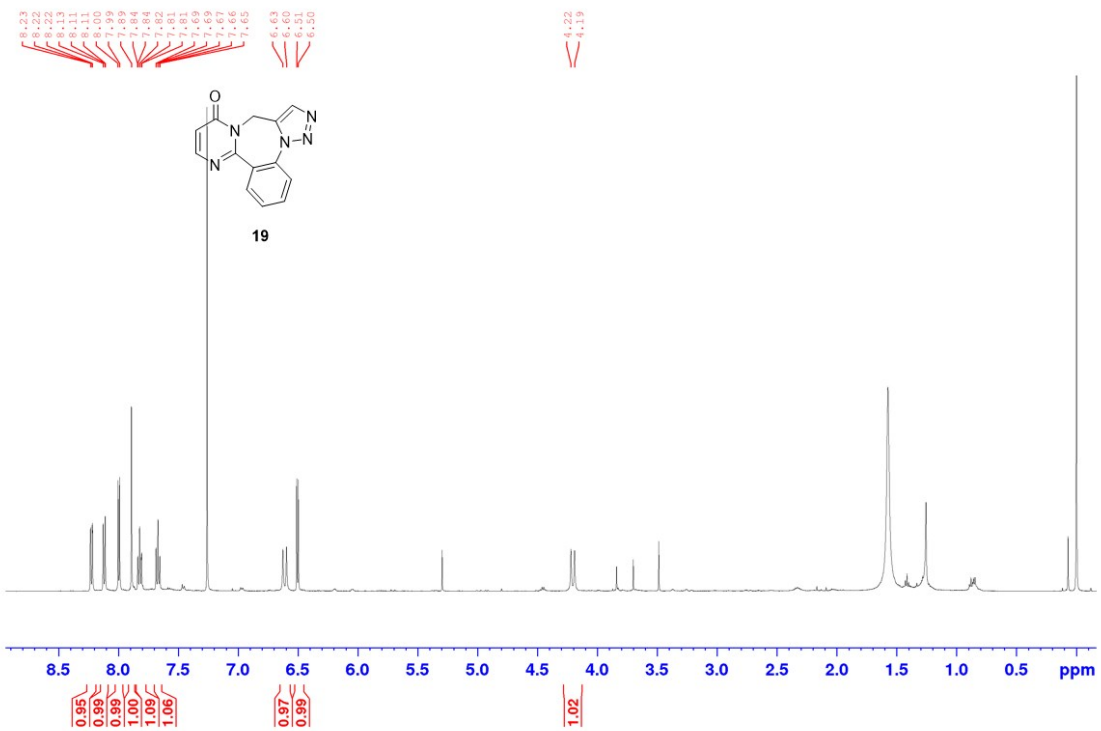
^{13}C NMR Spectrum of (*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-2-chloro-11a,12,15,15a,16,16a-hexa-hydro-12,15-methanobenzo[5,6][1,2,3]triazolo-[5',1':3,4][1,4]-diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-18b** ($CDCl_3$)



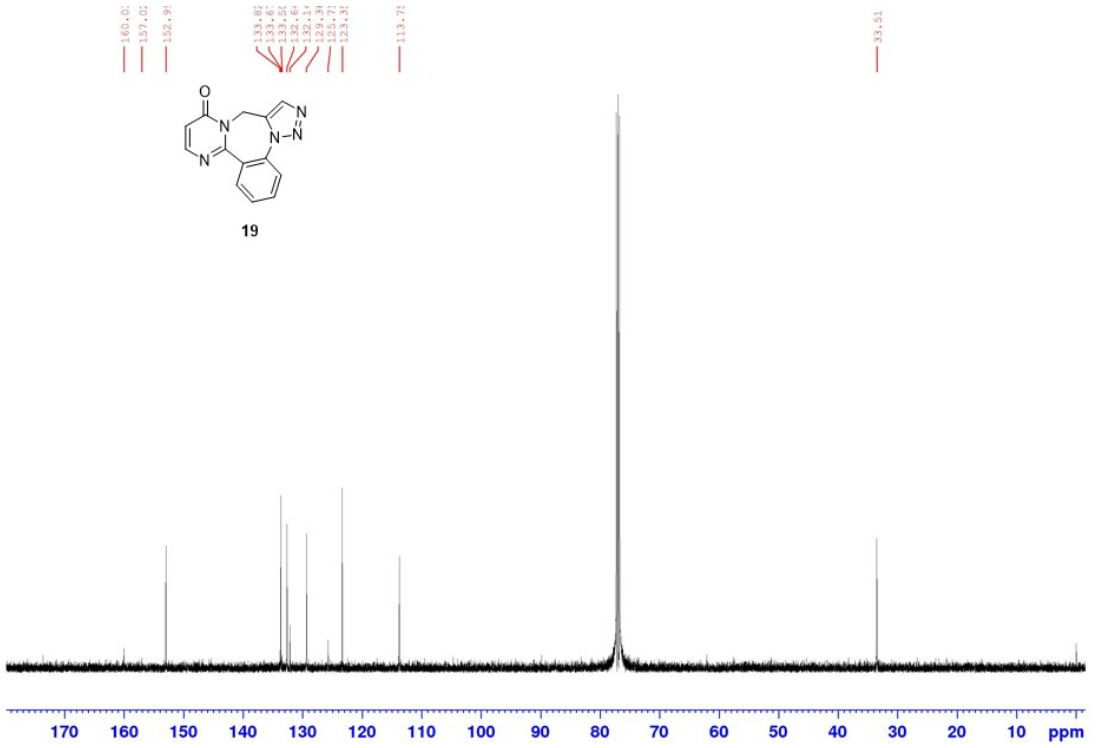
^{1}H NMR Spectrum of (*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]-diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-18c** ($CDCl_3$)



^{13}C NMR Spectrum of (*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-2-bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]-diazepino[7,1-*b*]quinazolin-11(9*H*)-one **(±)-18c** ($CDCl_3$)

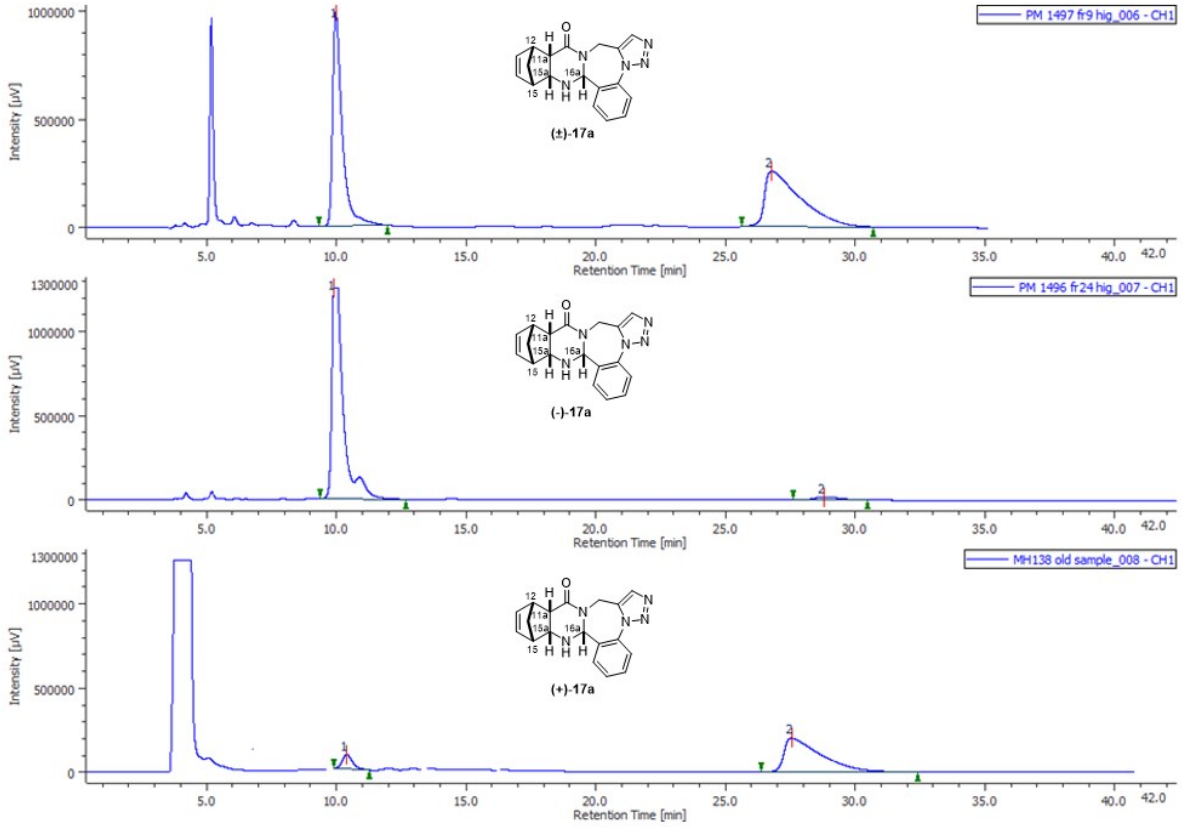


^{1}H NMR Spectrum of 9*H*-benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-11-one **19** ($CDCl_3$)



^{13}C NMR Spectrum of 9*H*-benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-11-one **19** ($CDCl_3$)

4**. HPLC chromatograms of domino products (±)-17a, (+)-17a and (–)-17a**



Chromatograms of racemic **(±)-17a** and enantiomeric domino products **(+)-17a** and **(–)-17a** determined by HPLC using Phenomenex-IA column [eluent: a mixture of *n*-hexane and IPA (60:40), flow rate: 0.5 mL·min^{-1}, detection by PDA detector, retention times (−)-**17a**: 9.98 min, (+)-**17a**: 28.77 min].

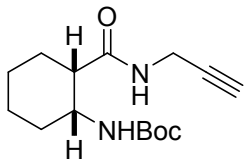
5. X-ray crystallography data for (±)-5a, (±)-6a and (±)-17c

Table 1. Crystal Data.

	(±)–**5a**	(±)–**6a**	(±)–**17c**
empirical formula	$C_{17}H_{19}N_5O$	$C_{17}H_{19}N_5O$	$C_{18}H_{16}BrN_5O$
fw	309.37	309.37	398.27
temp (K)	120(2)	120(2)	120(2)
λ(Å)	1.54184 Å	1.54184	1.54184
cryst syst space group	Monoclinic $P2_1/c$	Monoclinic $P2_1/c$	Monoclinic C2/c
a (Å)	11.5093(2)	10.95560(10)	21.0136(3)
b (Å)	13.0753(2)	8.17340(10)	8.39870(10)
c (Å)	10.9809(2	16.6676(2)	18.1668(3)
β (deg)	112.310(2)	98.8760(10)	100.948(2)
V (Å^3)	1528.79(5)	1474.62(3	3147.85(8)
Z	4	4	8
ρ_{calc} (Mg/m^3)	1.344	1.394	1.681
μ(Mo Kα) (mm^{-1})	0.709	0.735	3.710
No. reflns.	16866	20283	12301
Unique reflns.	3225	3120	3290
GOOF (F^2)	1.041	1.059	1.047
R_{int}	0.0263	0.0184	0.0205
R1[a] ($I \geq 2\sigma$)	0.0356	0.0350	0.0216
wR2[b] ($I \geq 2\sigma$)	0.0935	0.0900	0.0557

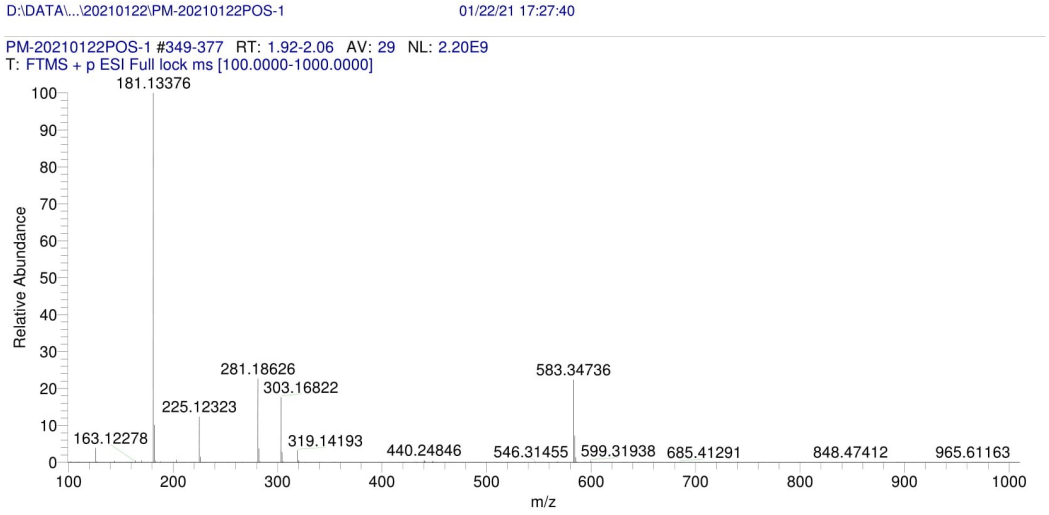
[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

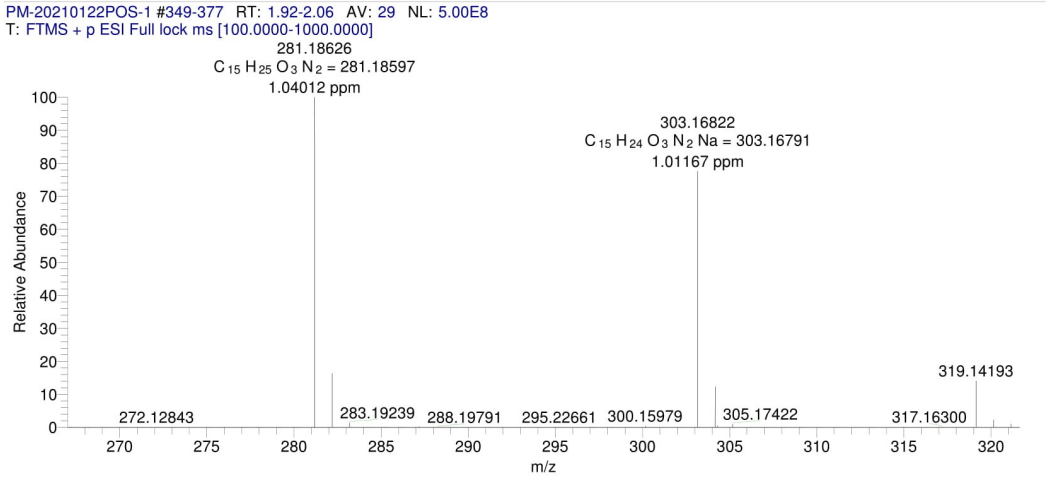
6. Copies of HRMS-ESI Spectra

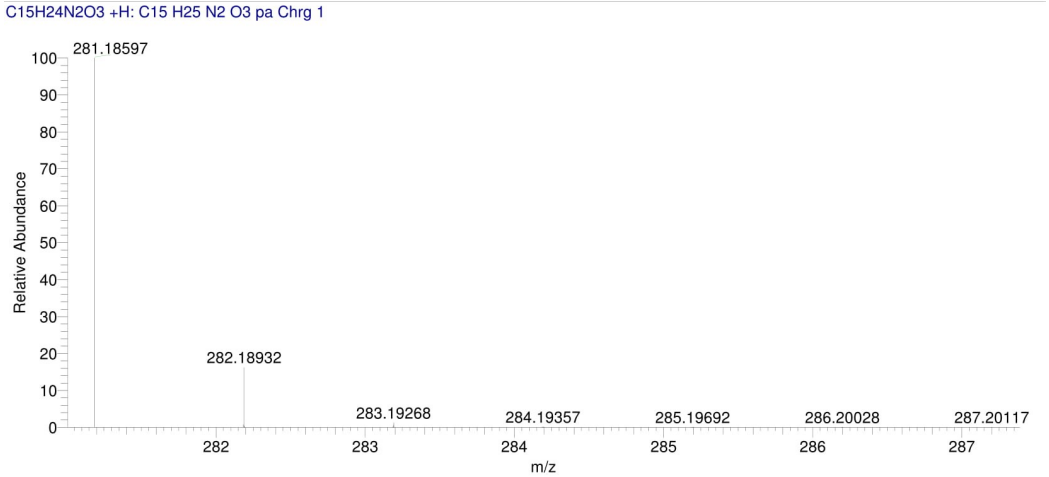


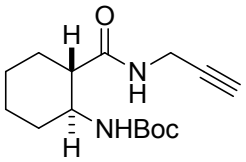
(±)-3

tert-Butyl (*cis*-2-(prop-2-yn-1-ylcarbamoyl)cyclohexyl)carbamate (±)-3:



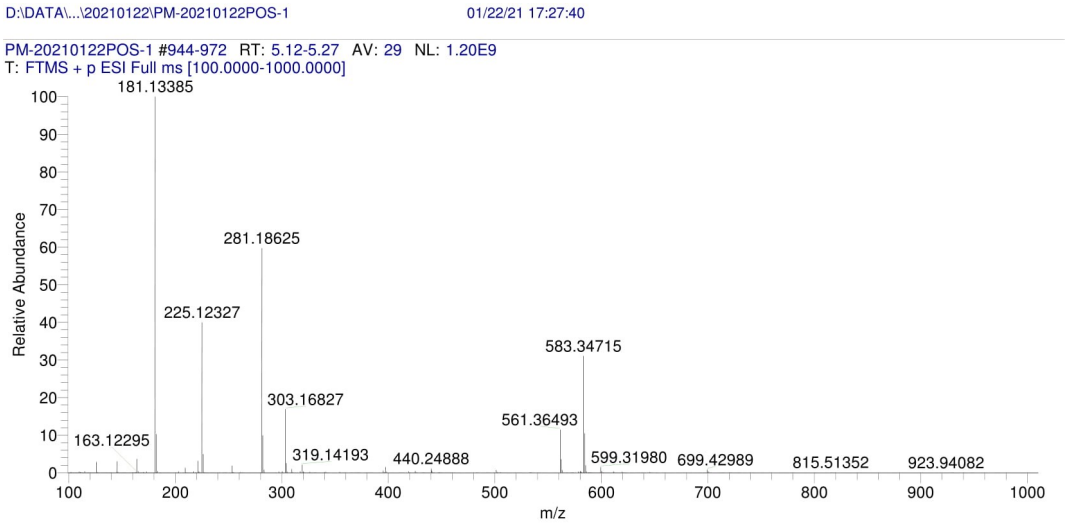


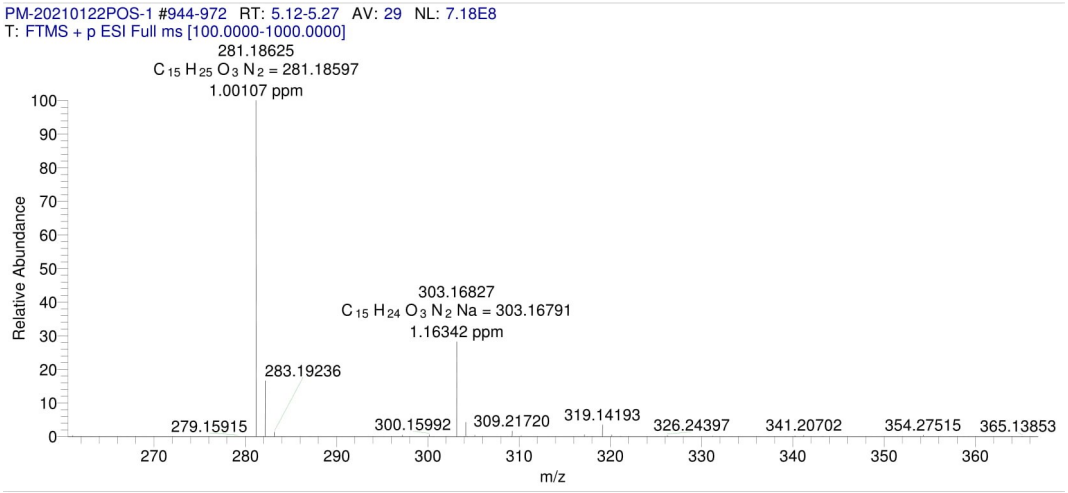


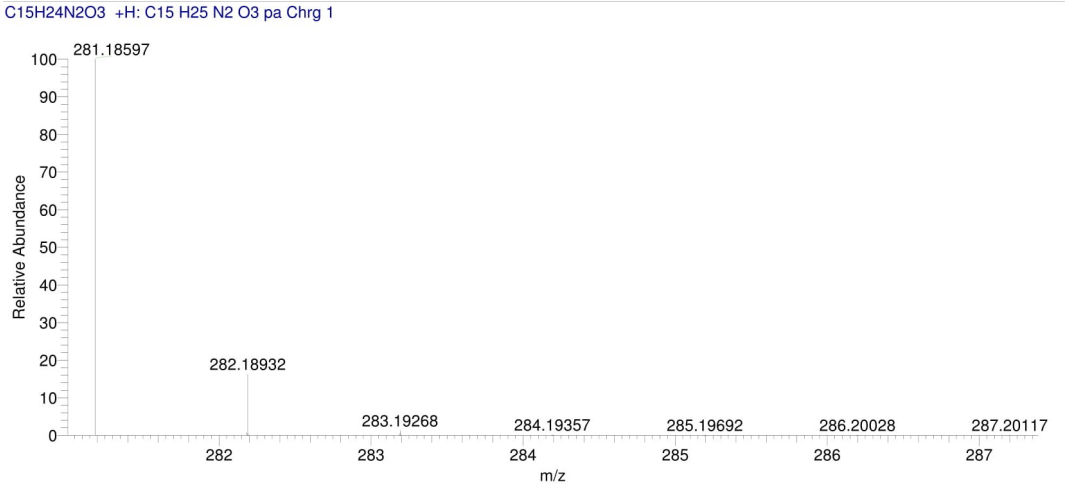


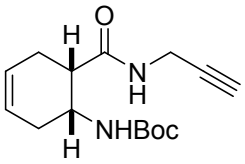
(±)-4

***tert*-Butyl (*trans*-2-(prop-2-yn-1-ylcarbamoyl)cyclohexyl)carbamate (±)-4:**



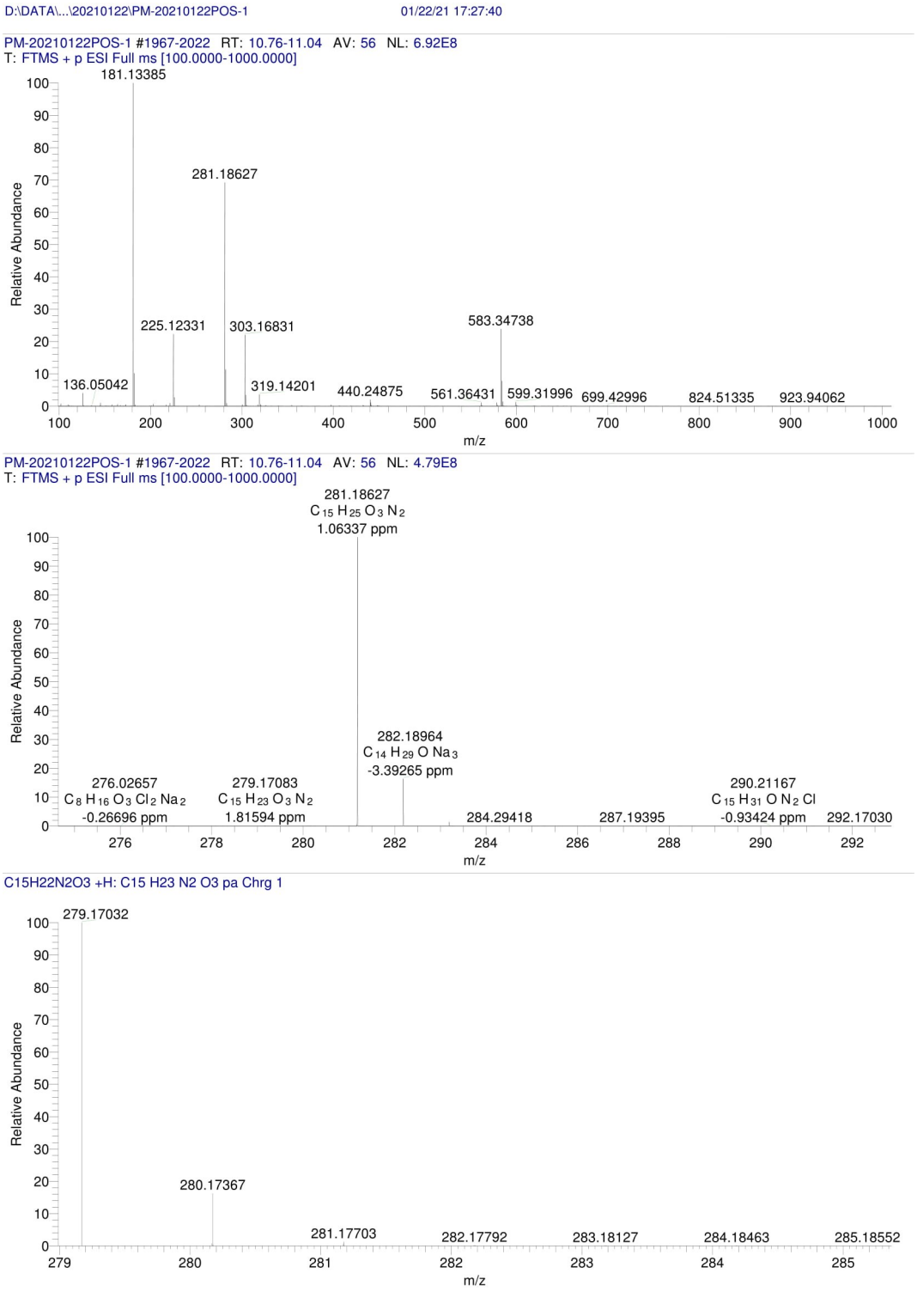


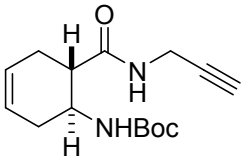




(±)-9

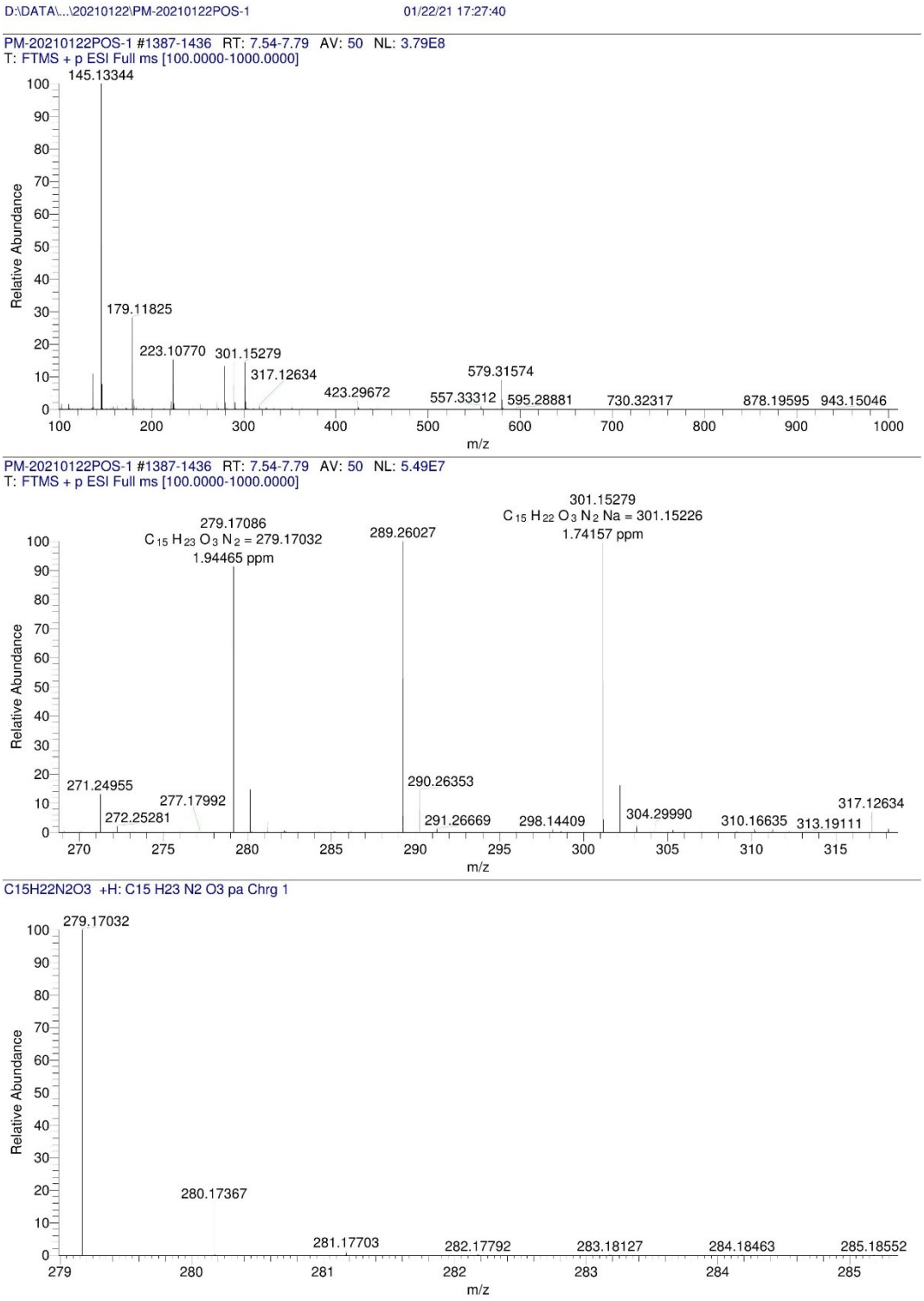
tert-Butyl (*cis*-6-(prop-2-yn-1-ylcarbamoyl)cyclohex-3-en-1-yl)carbamate (±)-9:

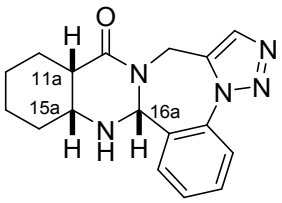




(±)-10

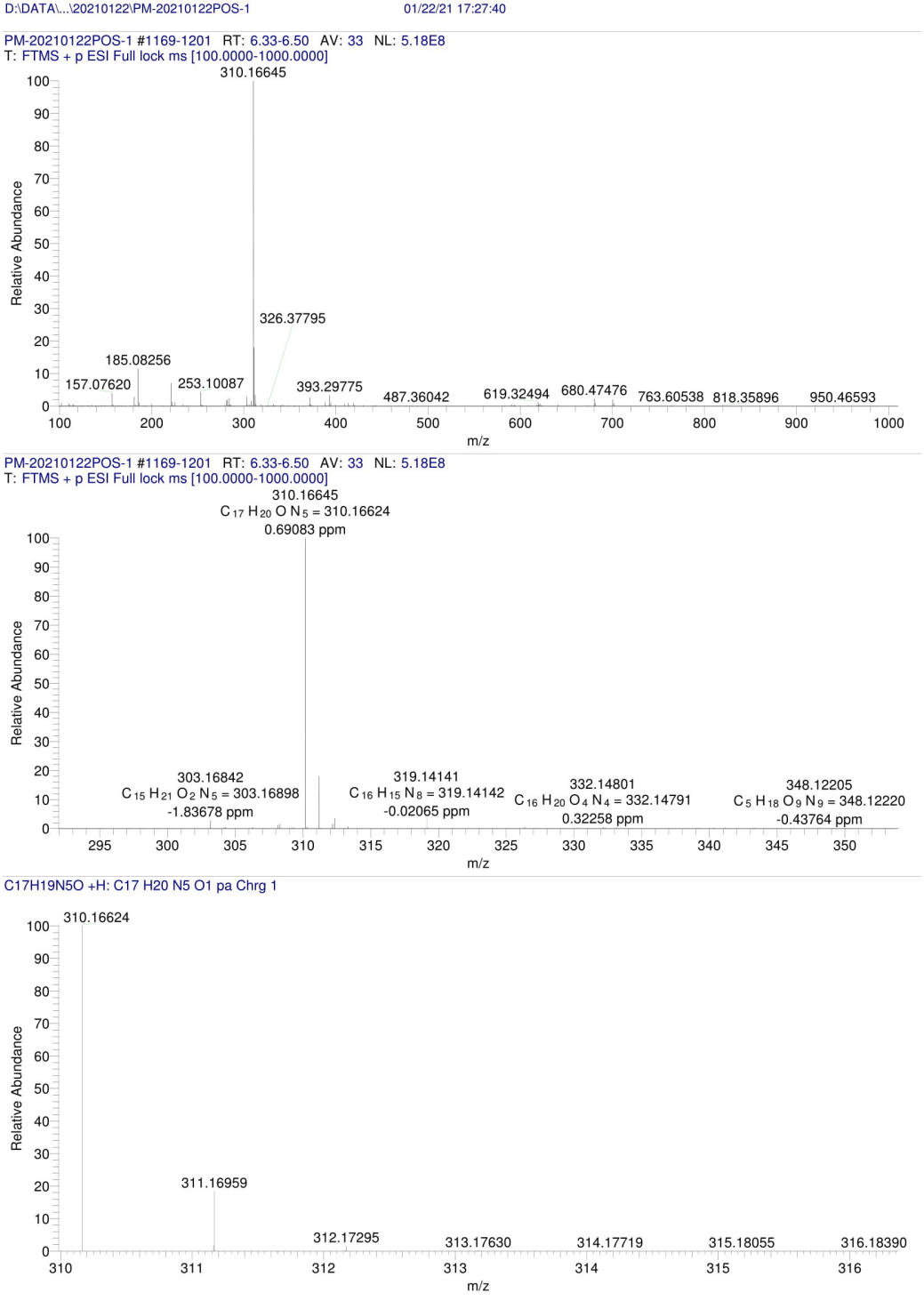
***tert*-Butyl (*trans*-6-(prop-2-yn-1-ylcarbamoyl)cyclohex-3-en-1-yl)carbamate (±)-10:**

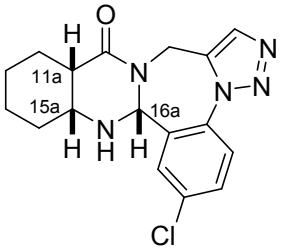




(±)-5a

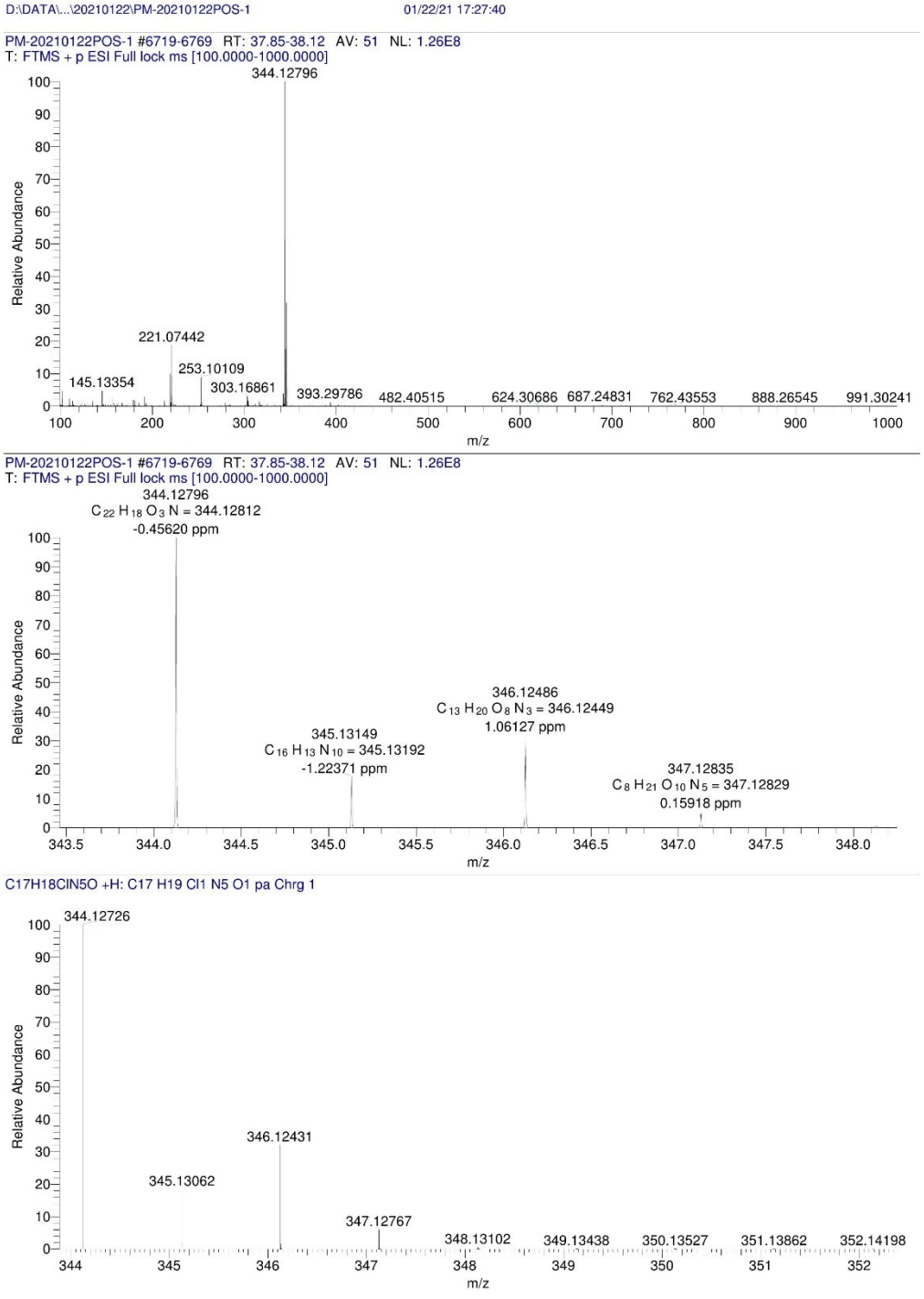
(*r*-11a,*c*-15a,*c*-16a)-11a,12,13,14,15,15a,16,16a-Octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-5a:

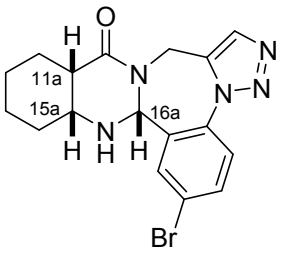




(±)-5b

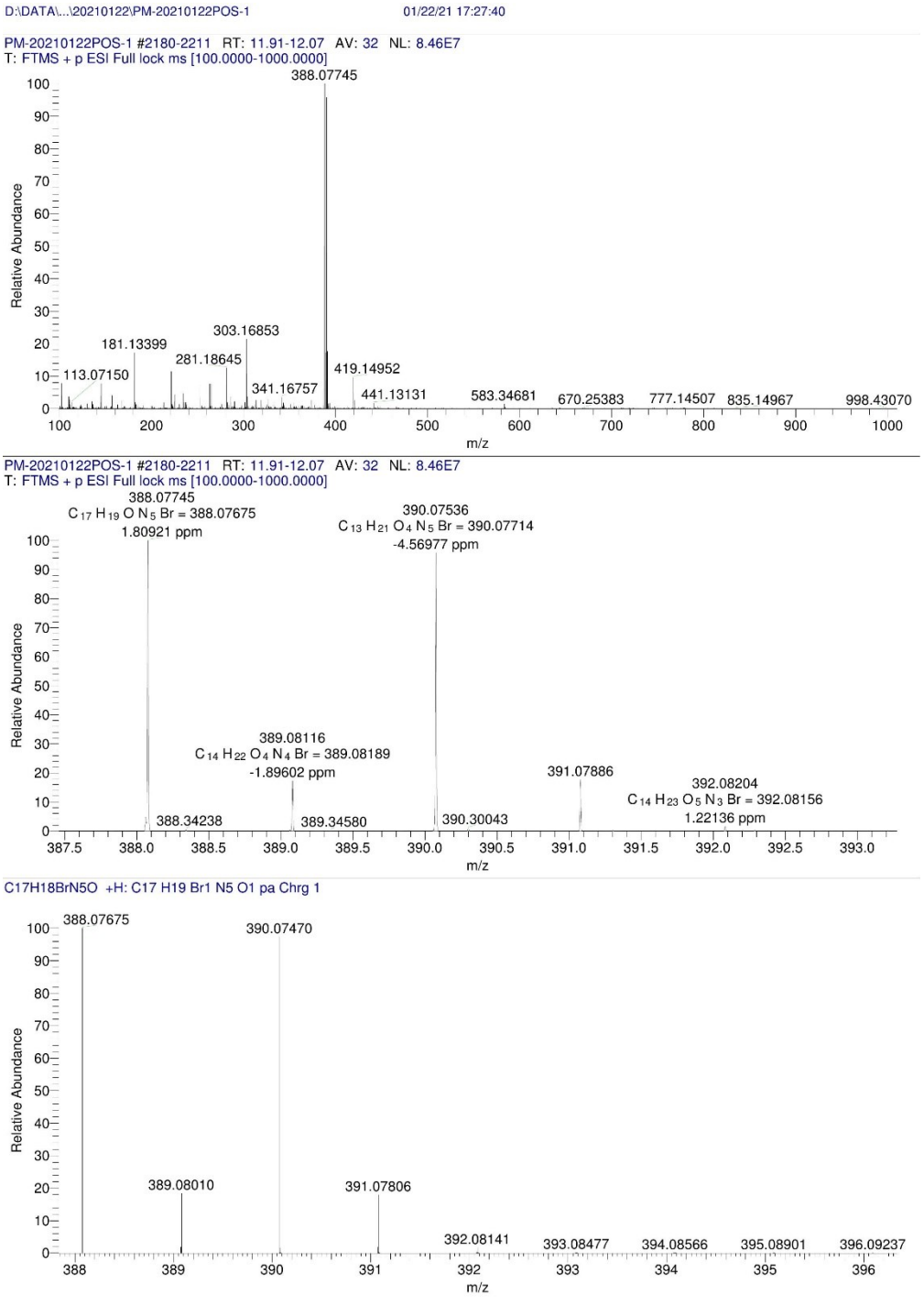
(*r*-11a,*c*-15a,*c*-16a)-2-Chloro-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-5b:

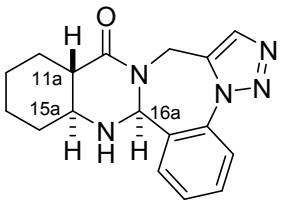




(±)-5c

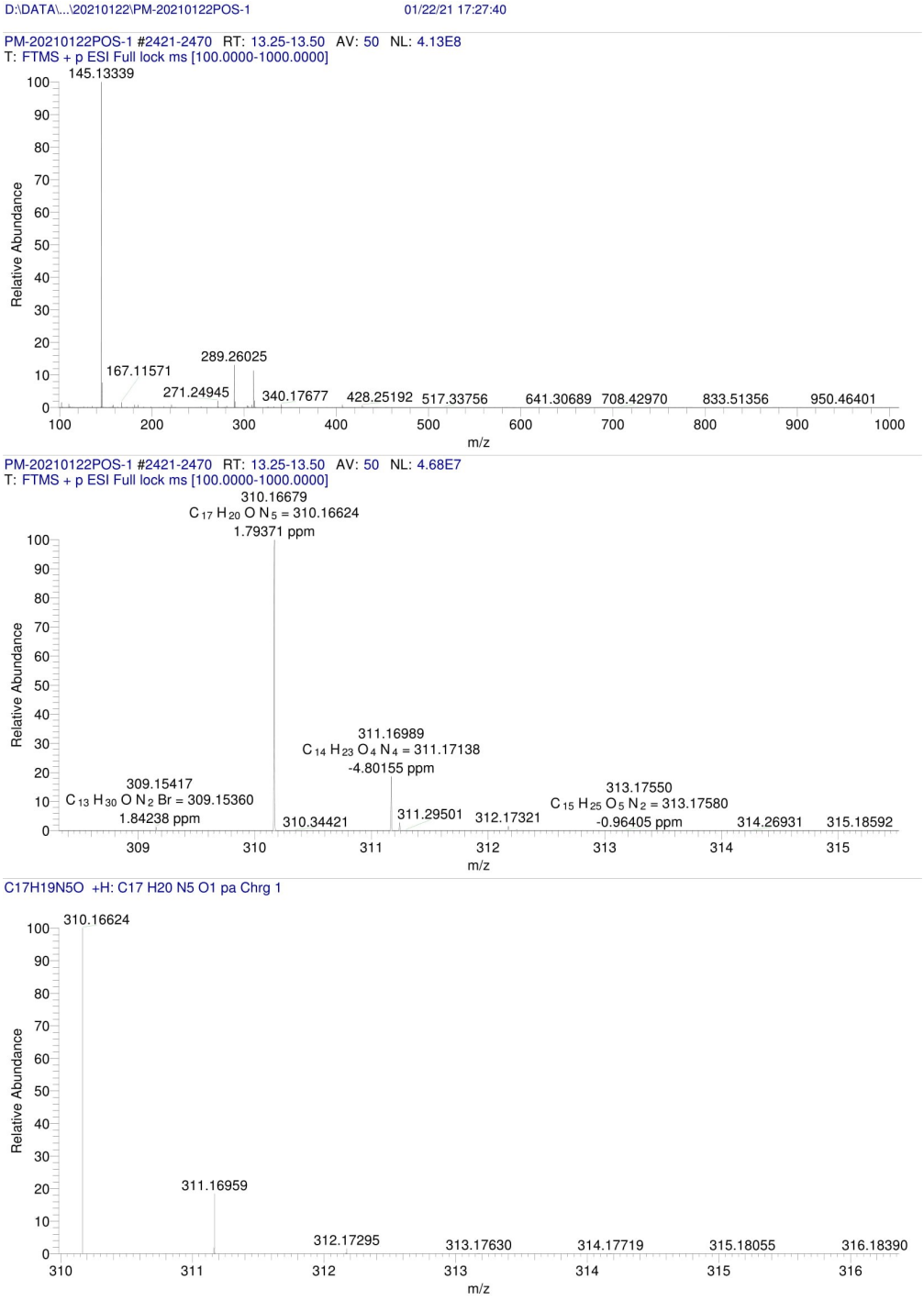
(*r*-11a,*c*-15a,*c*-16a)-2-Bromo-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-5c:

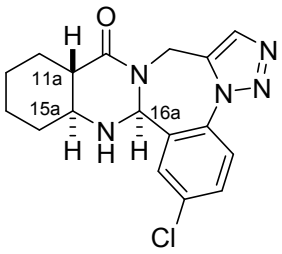




(±)-6a

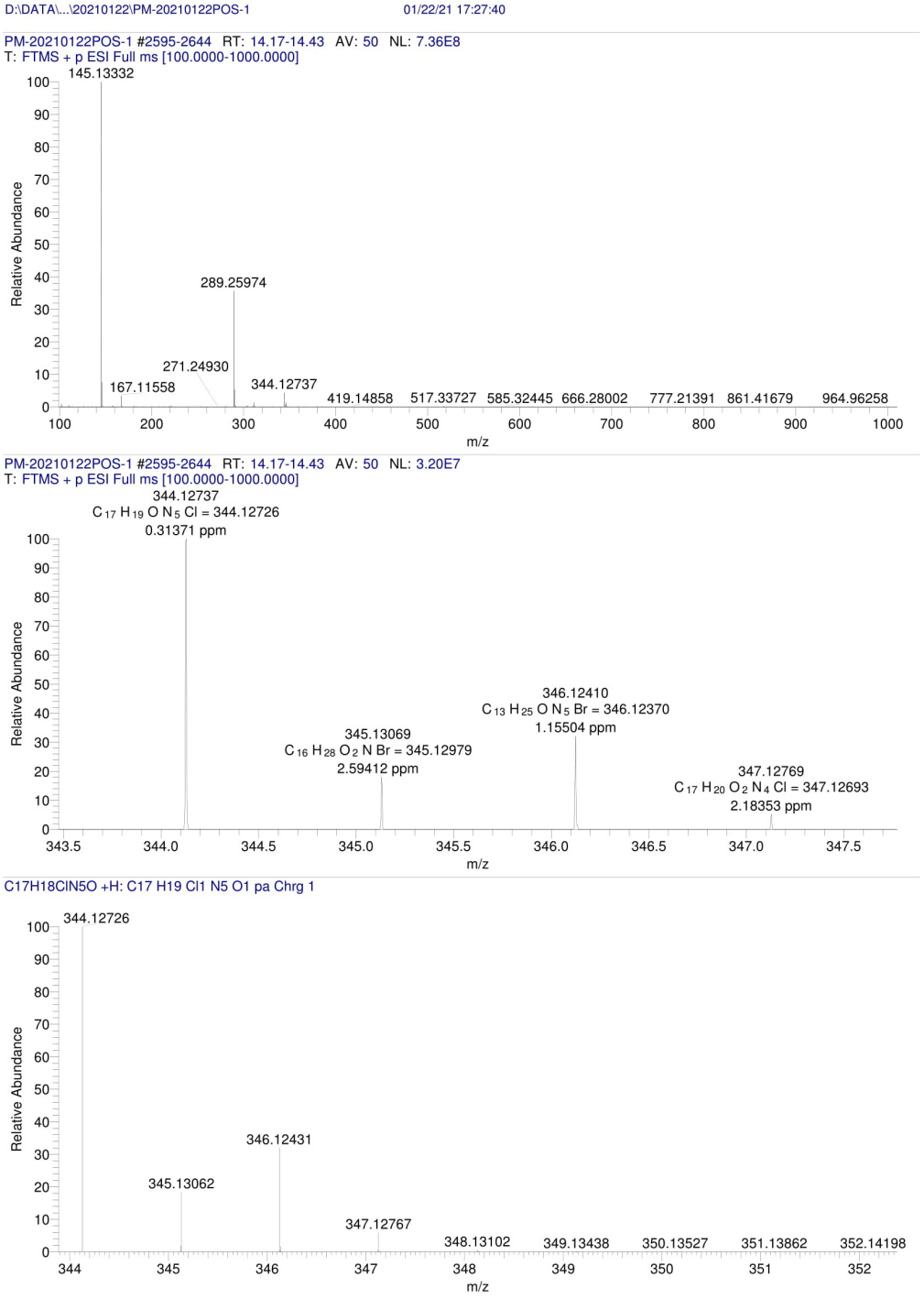
(*r*-11a,*t*-15a,*t*-16a)-11a,12,13,14,15,15a,16,16a-Octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-6a:

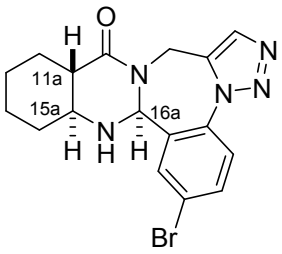




(±)-6b

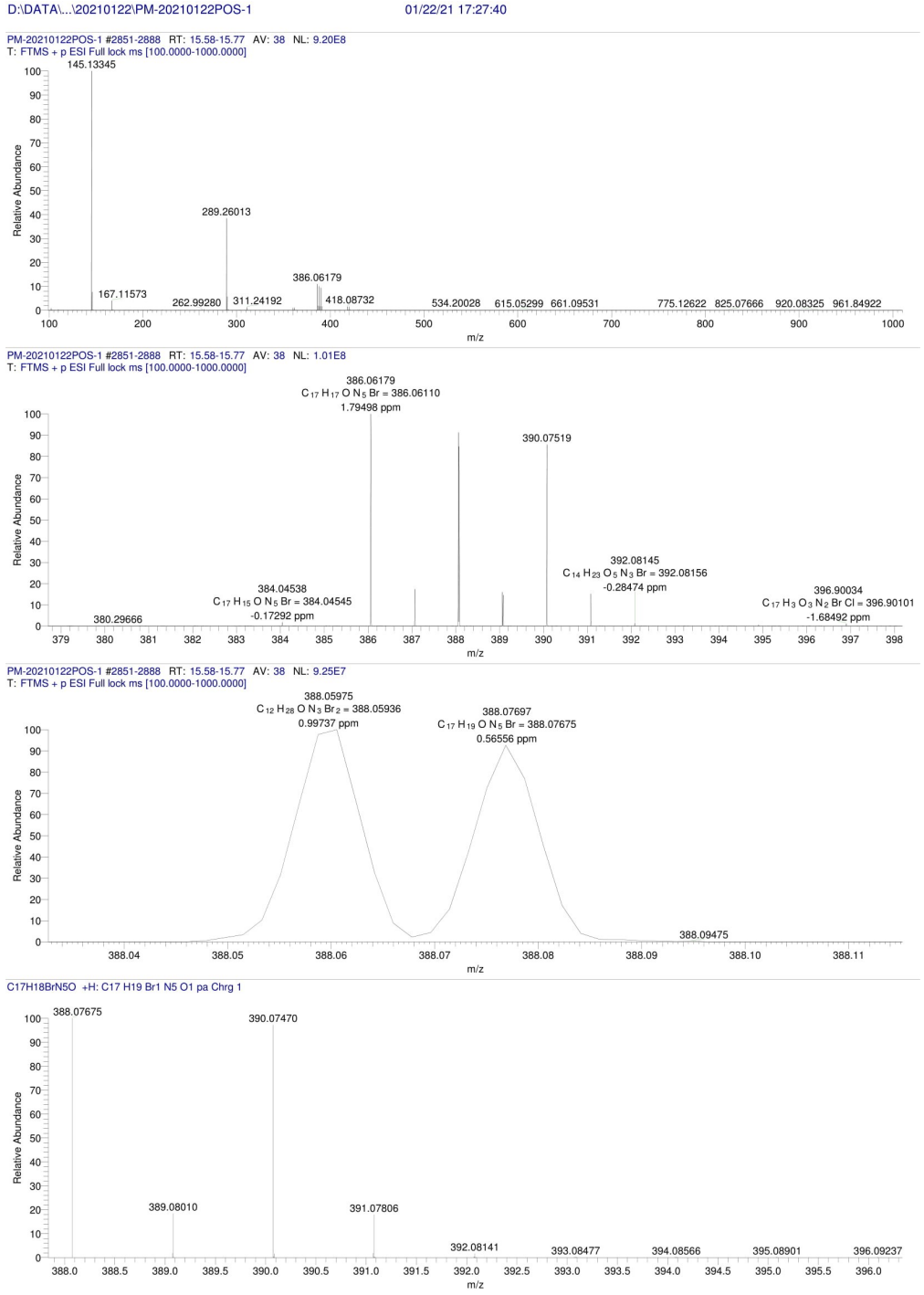
(*r*-11a,*t*-15a,*t*-16a)-2-Chloro-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-6b:

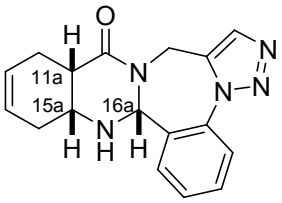




(±)-6c

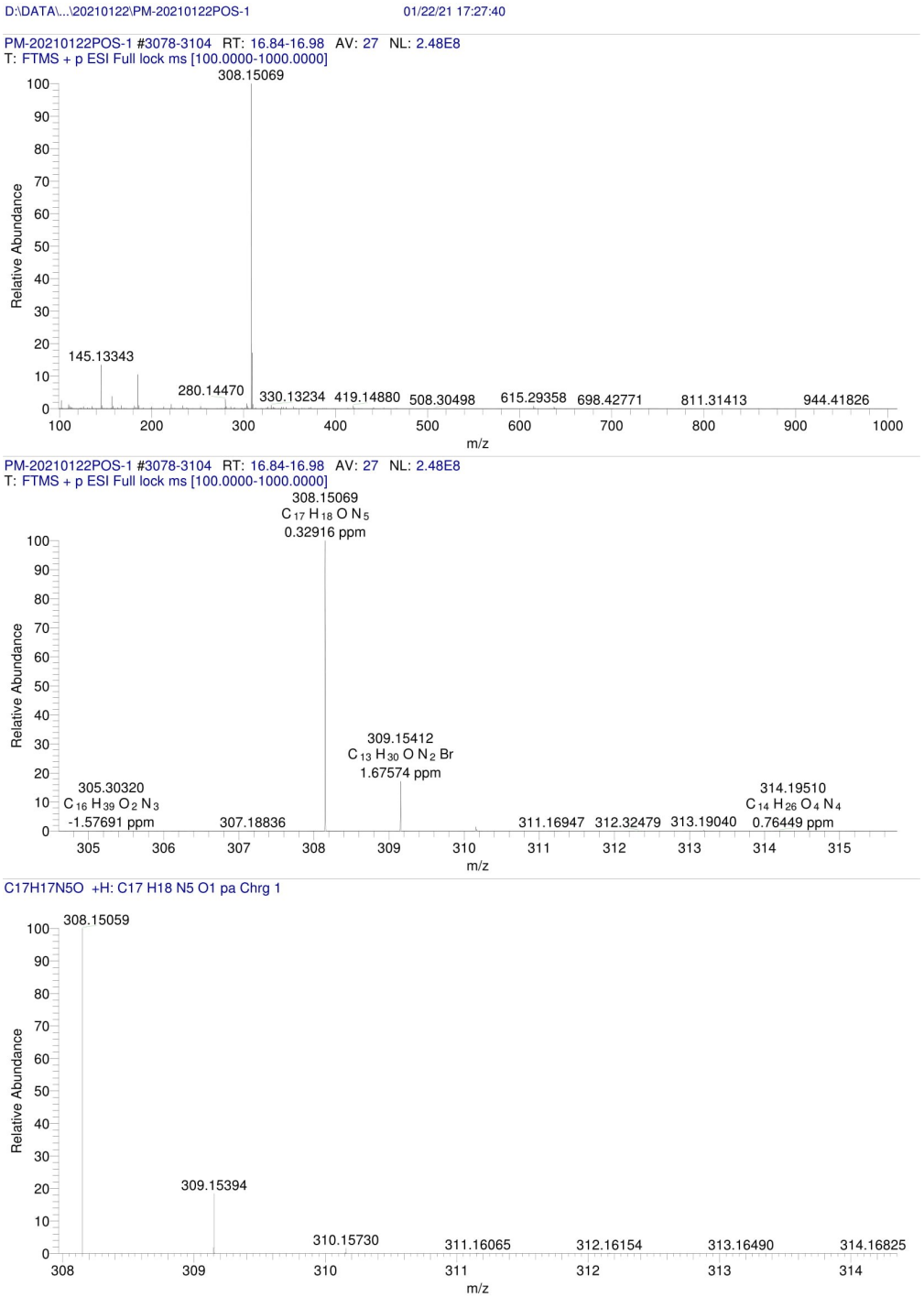
(*r*-11a,*t*-15a,*t*-16a)-2-Bromo-11a,12,13,14,15,15a,16,16a-octahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-6c:

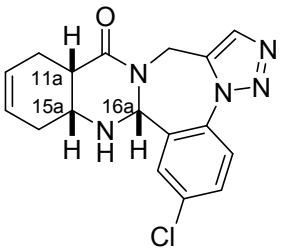




(±)-11a

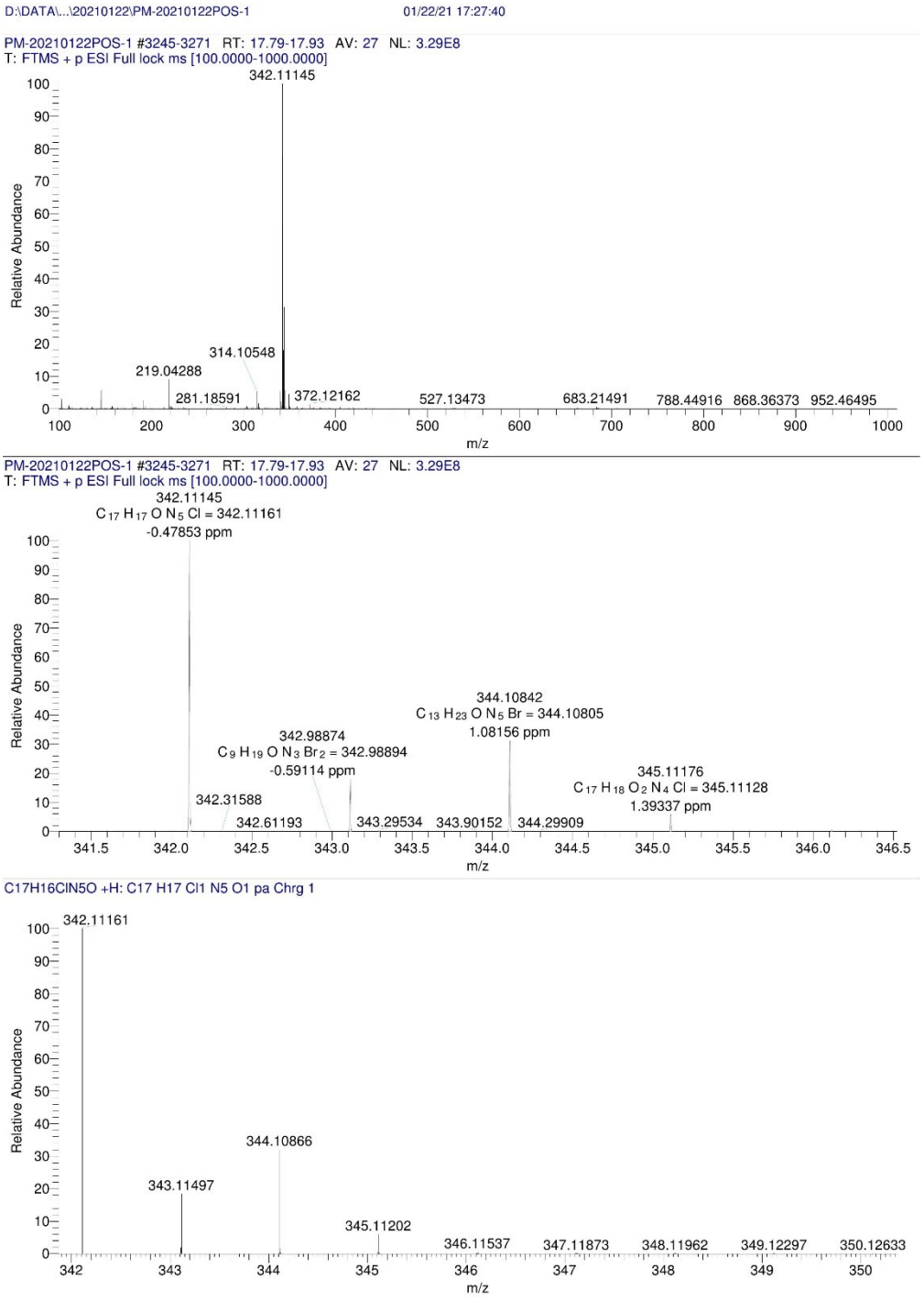
(*r*-11a,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-Hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-11a:

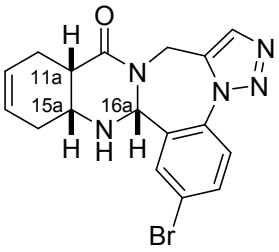




(±)-11b

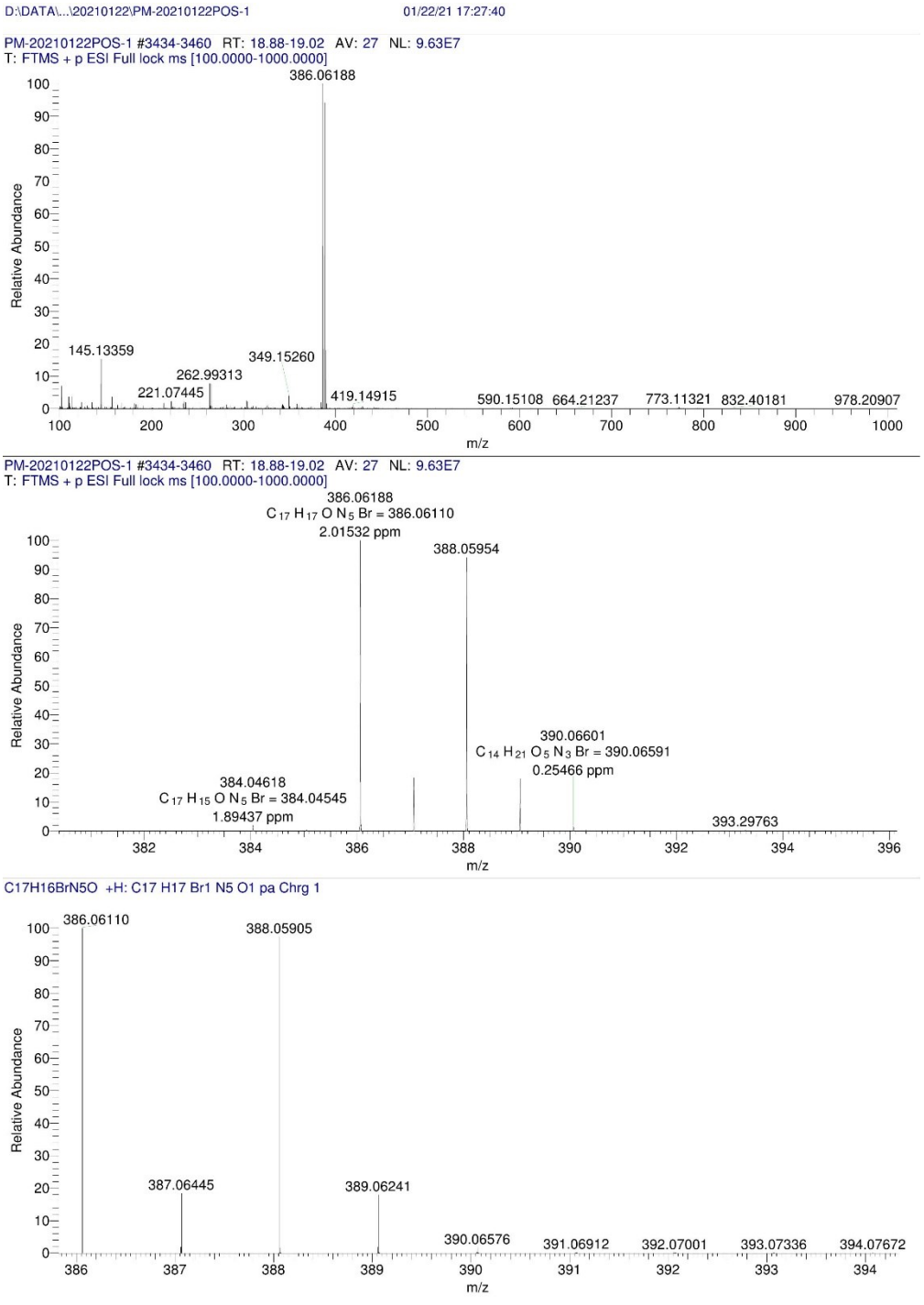
(*r*-11a,*c*-15a,*c*-16a)-2-Chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-11b:

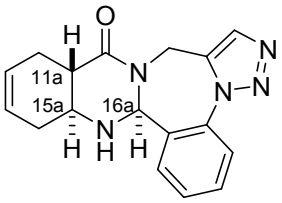




(±)-11c

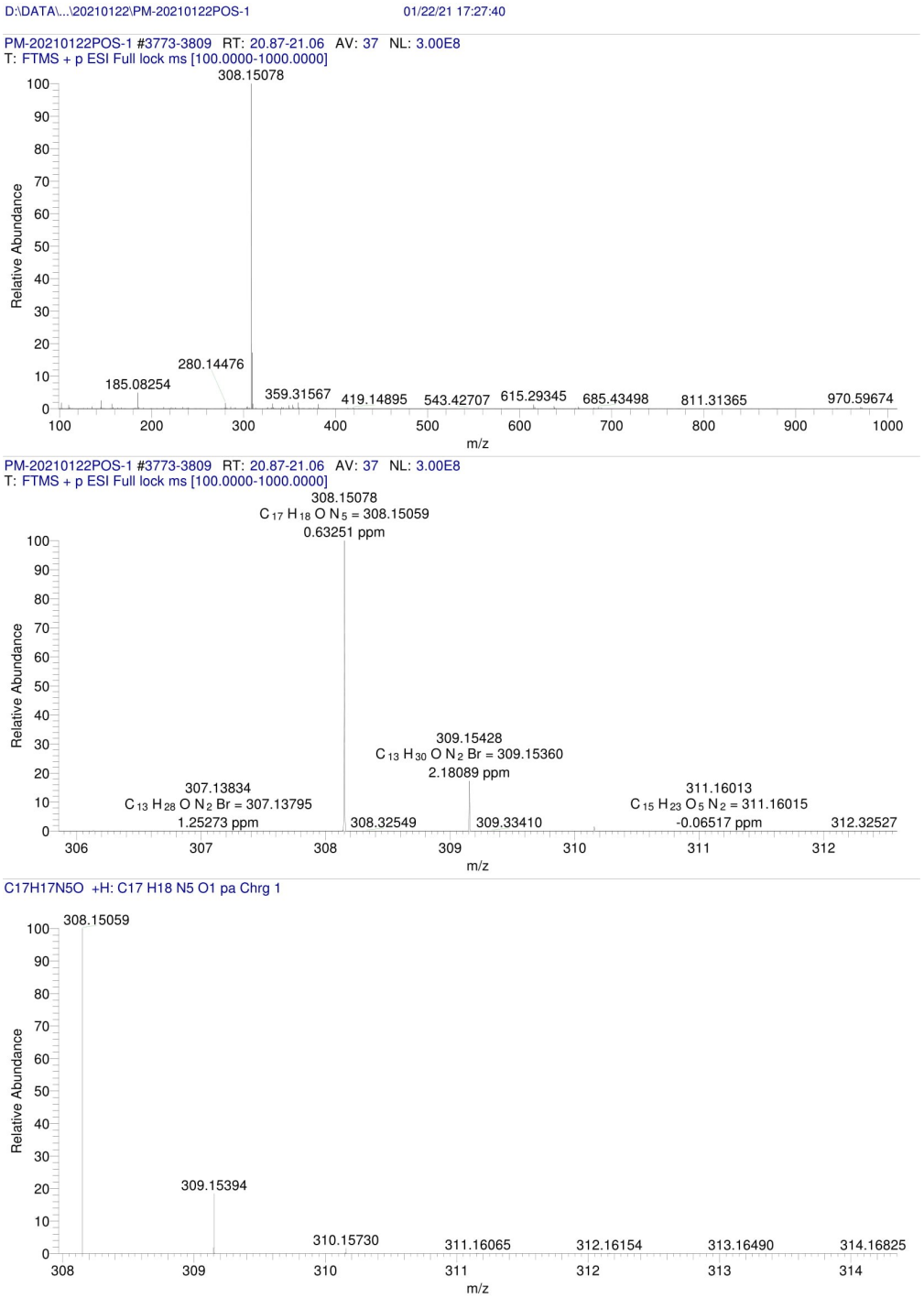
(*r*-11a,*c*-15a,*c*-16a)-2-Bromo-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-11c:

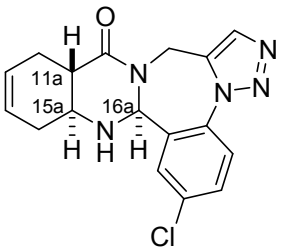




(±)-12a

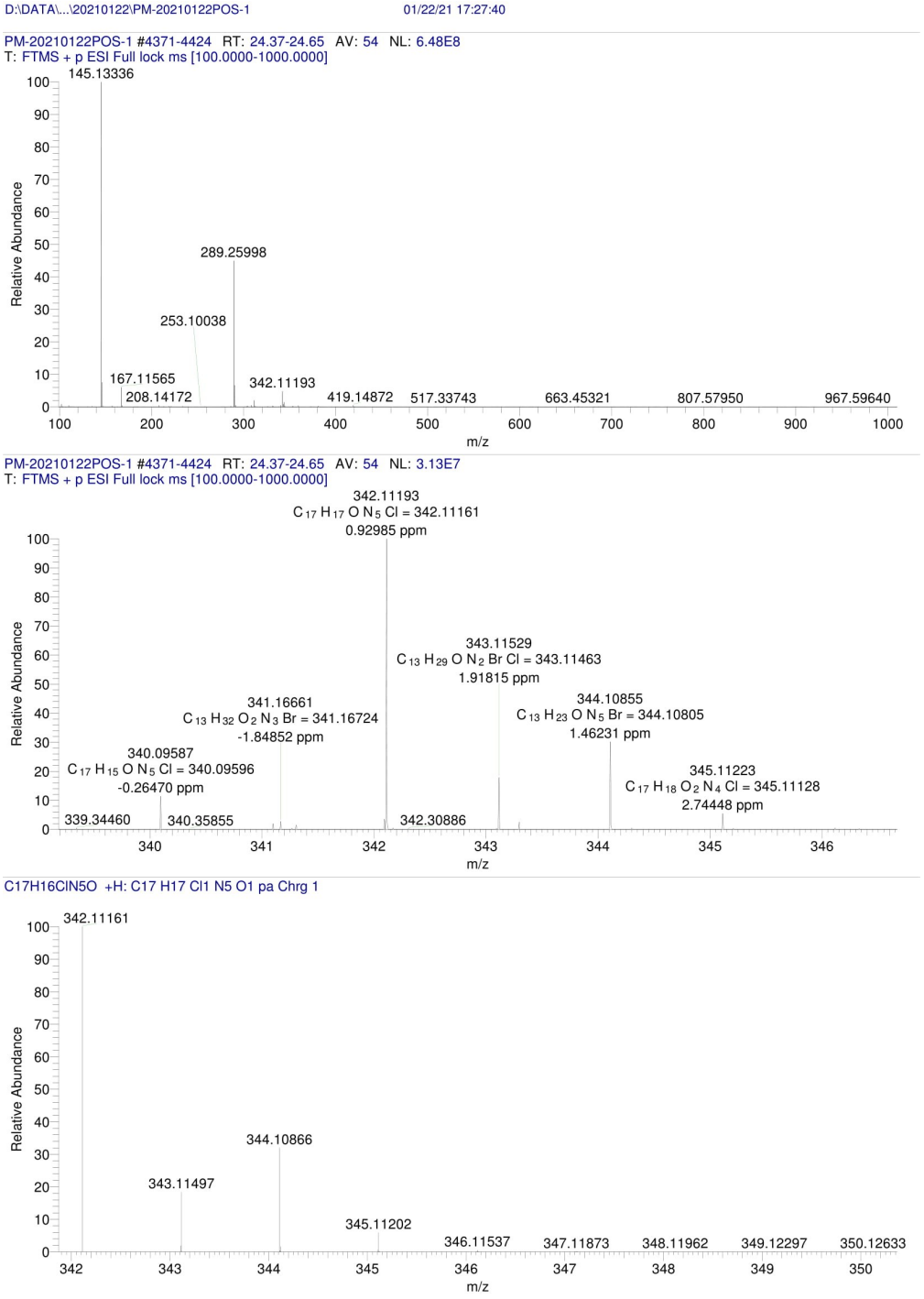
(*r*-11a,*t*-15a,*t*-16a)-11a,12,15,15a,16,16a-Hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-12a:

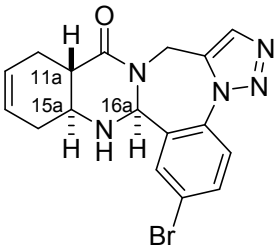




(±)-12b

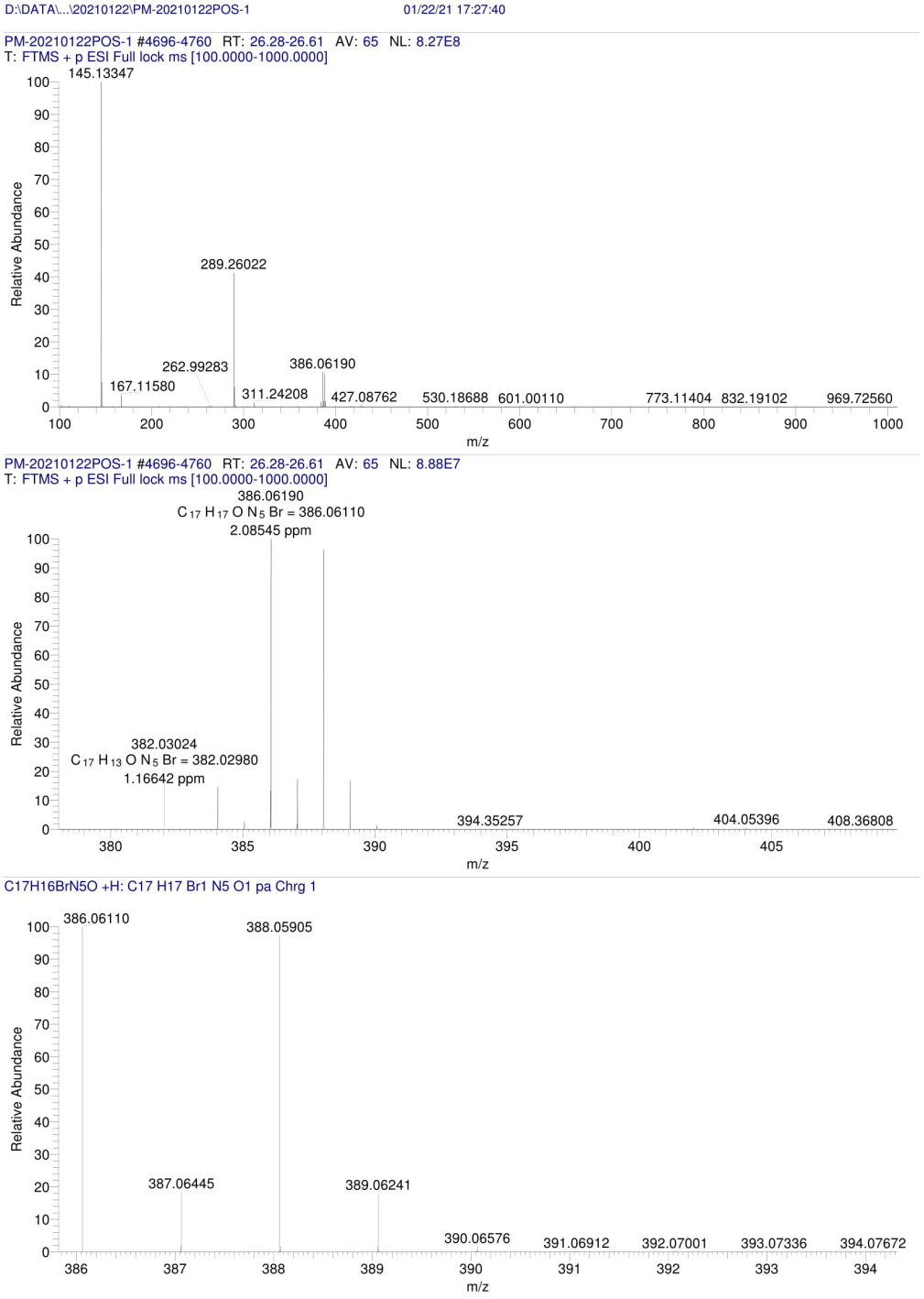
(*r*-11a,*t*-15a,*t*-16a)-2-Chloro-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-12b:

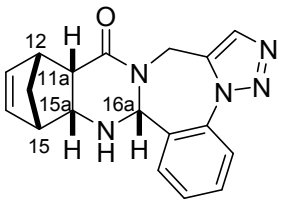




(±)-12c

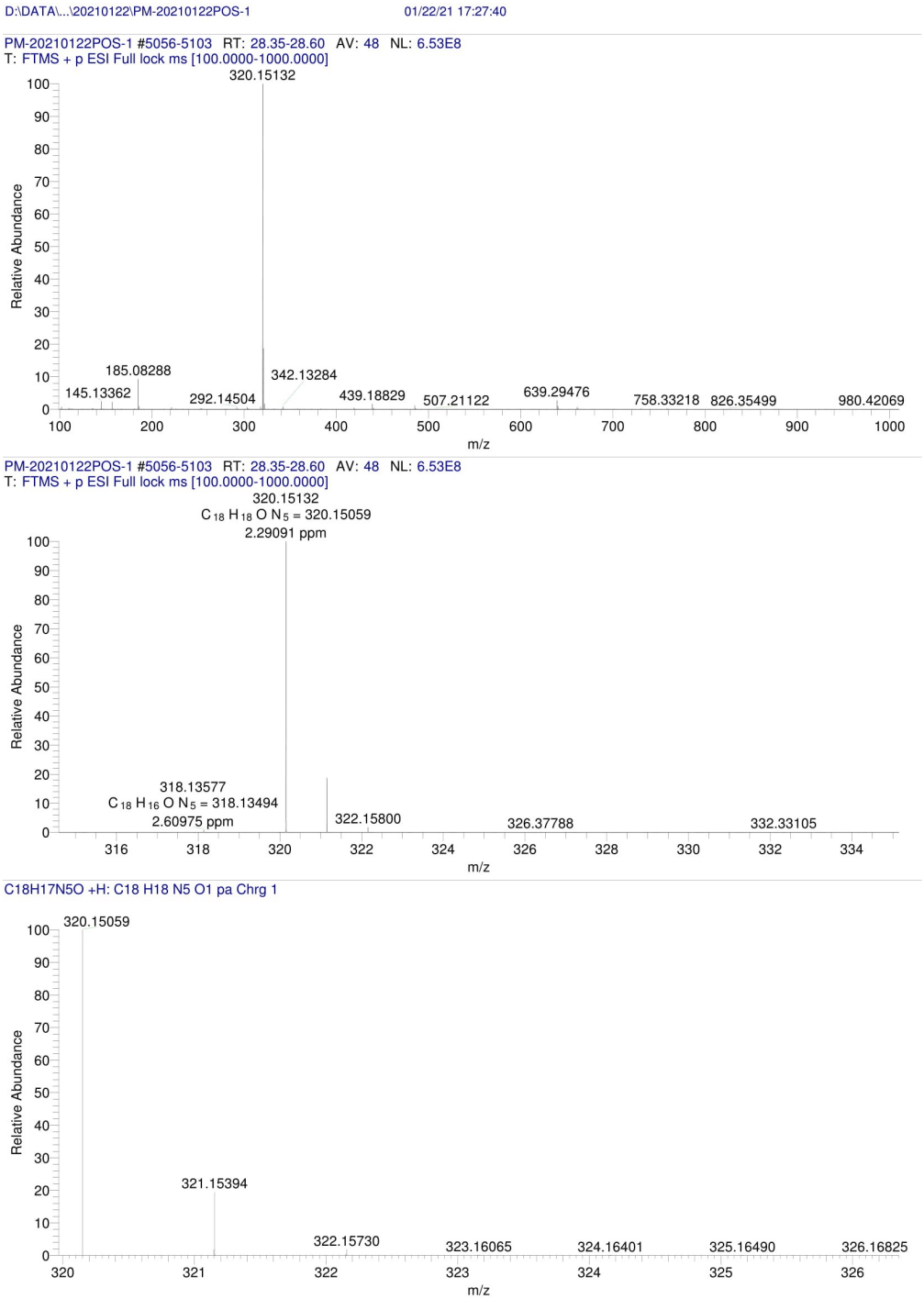
(*r*-11a,*t*-15a,*t*-16a)-2-Bromo-11a,12,15,15a,16,16a-hexahydrobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-b]quinazolin-11(9*H*)-one (±)-12c:

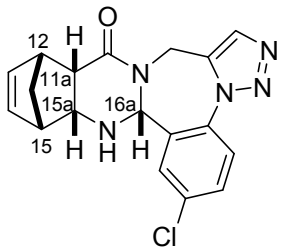




(±)-17a

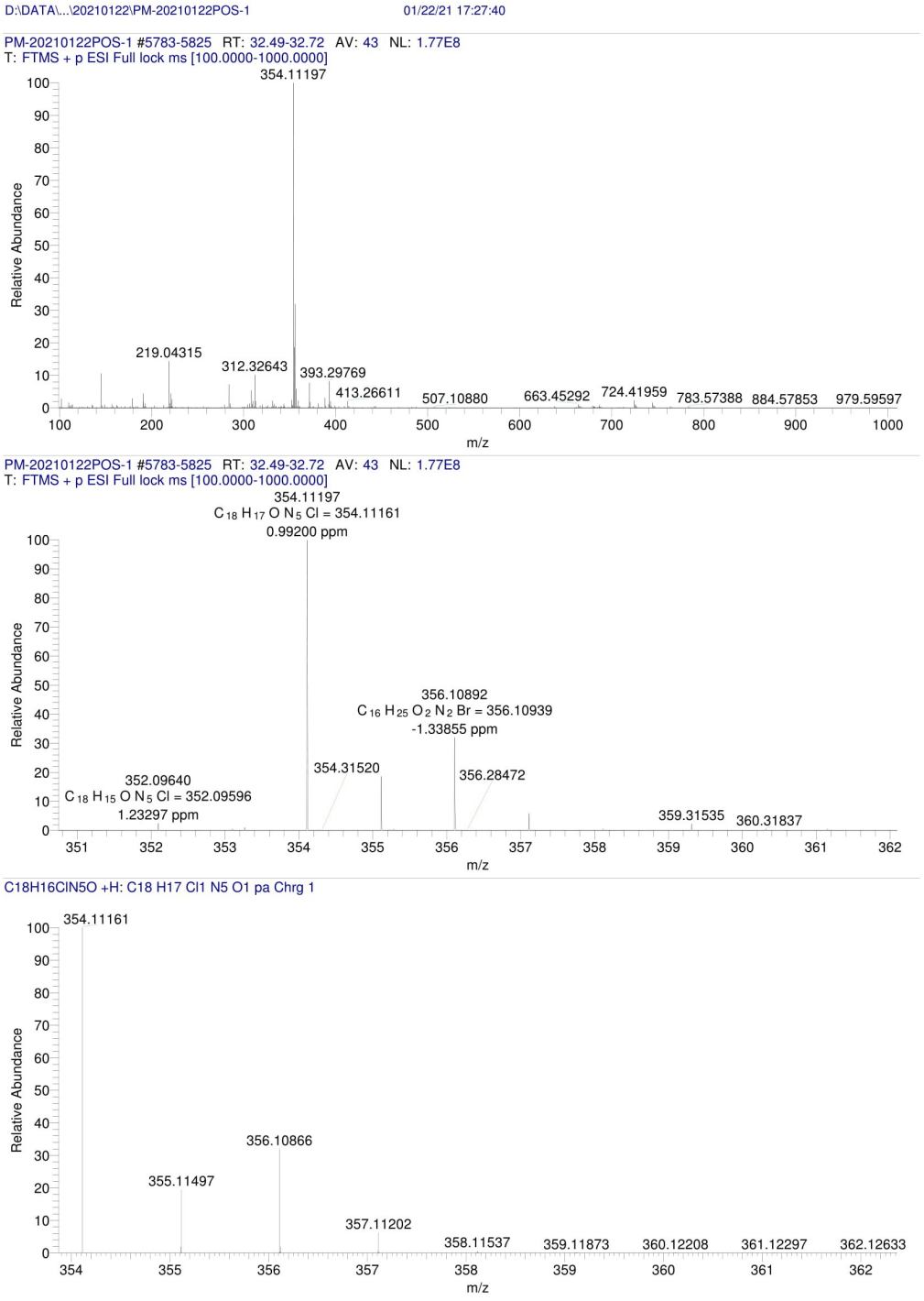
(*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-hexahydro-12,15-Methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-17a:

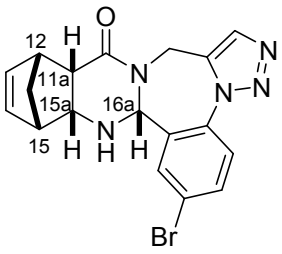




(±)-17b

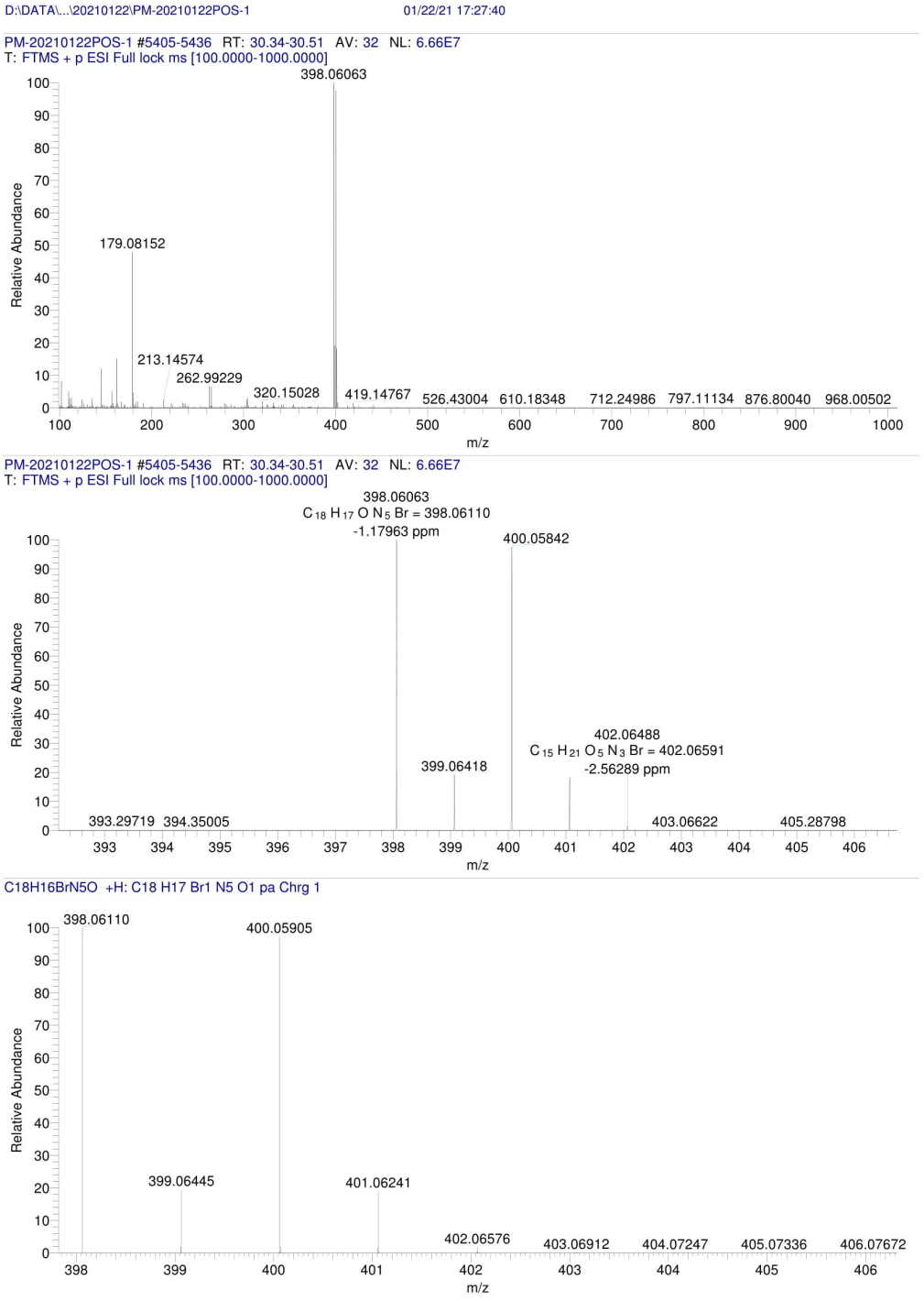
(*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-Chloro-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-17b:

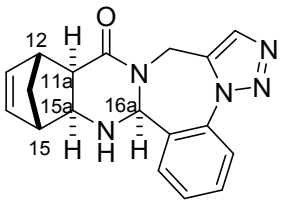




(±)-17c

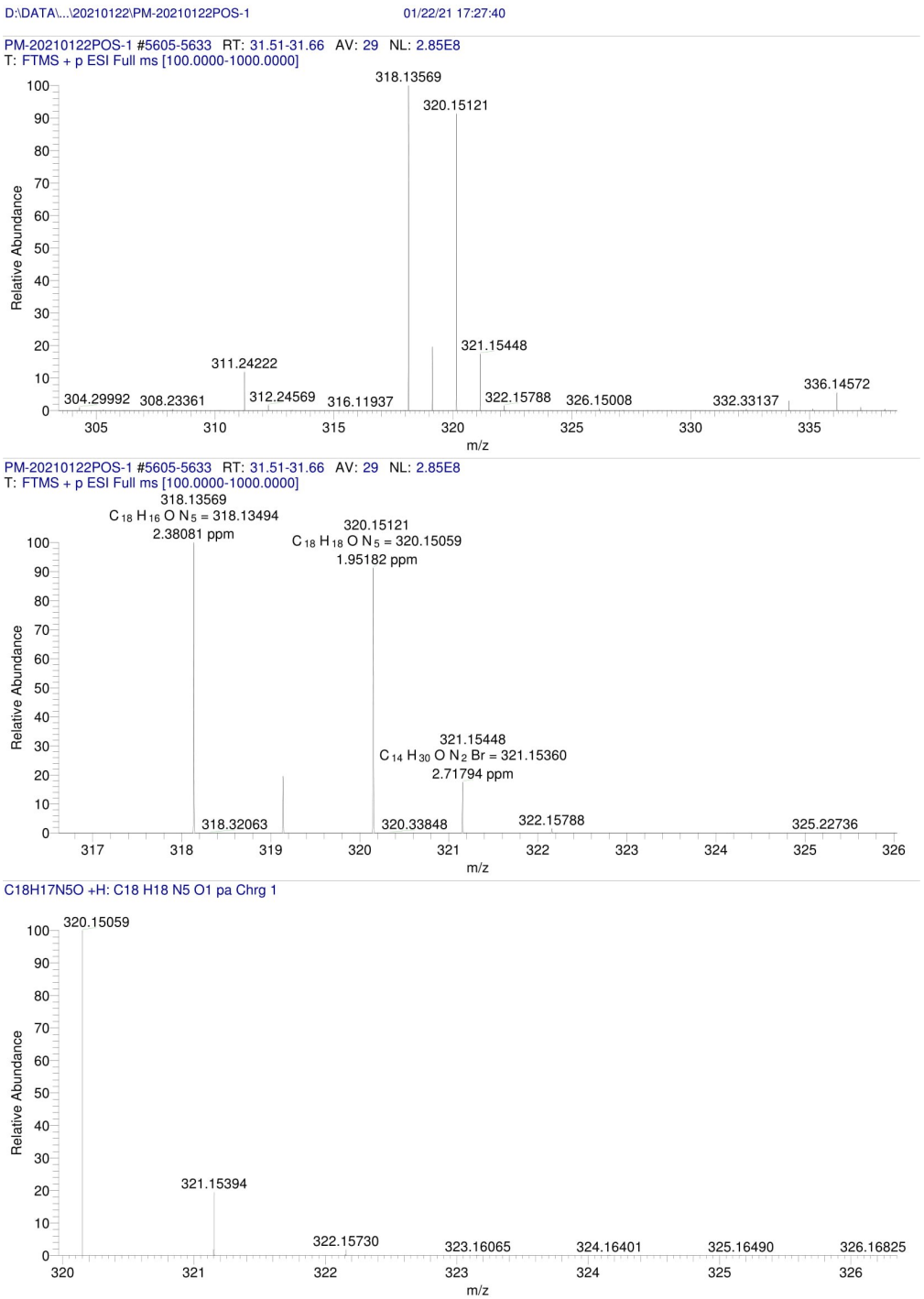
(*r*-11a,*t*-12,*t*-15,*c*-15a,*c*-16a)-2-Bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-17c:

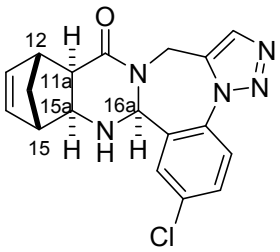




(±)-18a

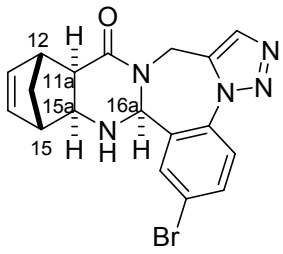
(*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-11a,12,15,15a,16,16a-Hexahydro-12,15 methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]diazepino[7,1-*b*]-quinazolin-11(9*H*)-one (±)-18a:





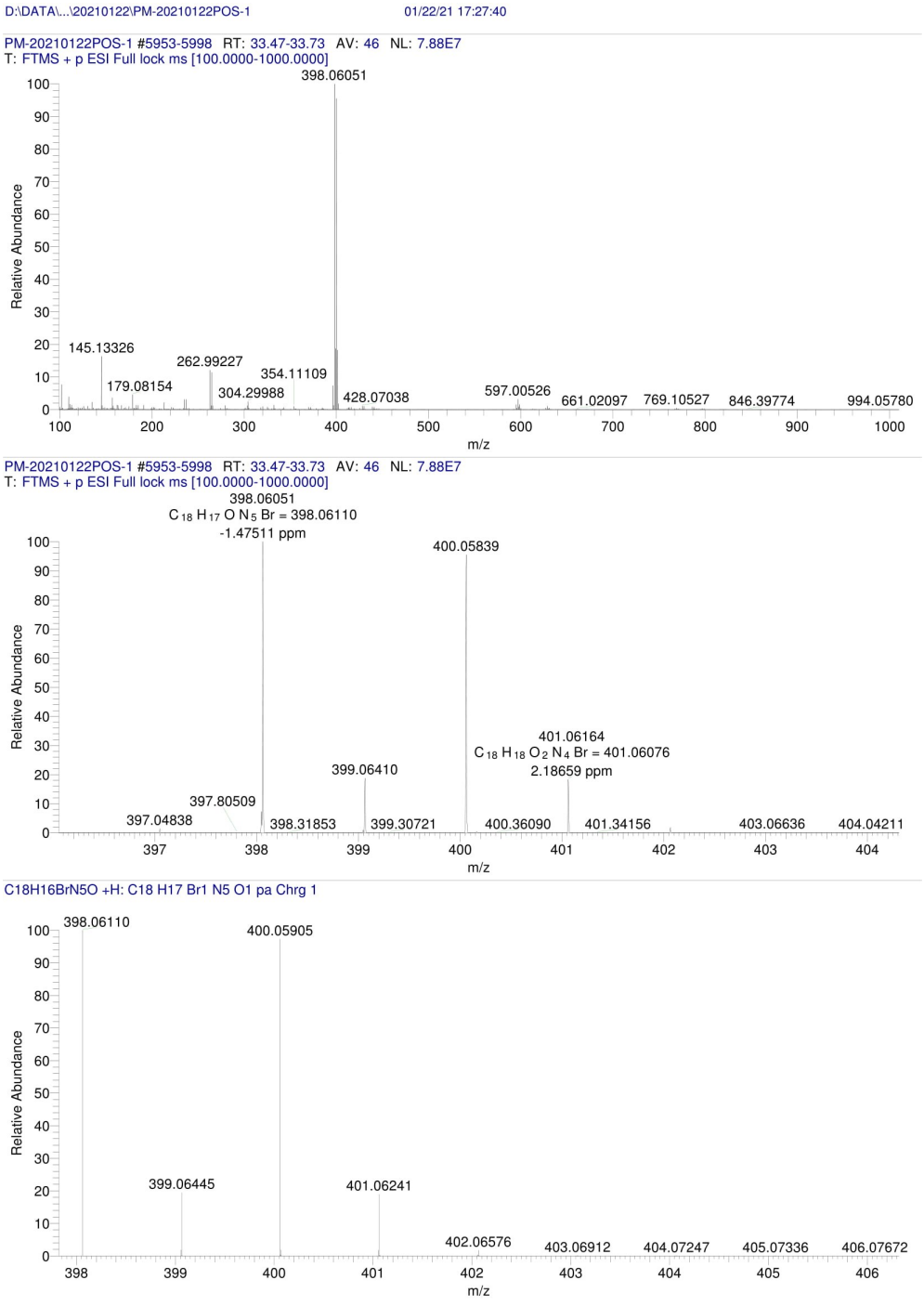
(±)-18b

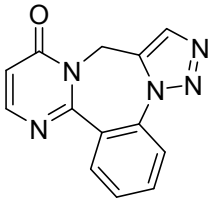
(*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-2-Chloro-11a,12,15,15a,16,16a-hexa-hydro-12,15-methanobenzo[5,6][1,2,3]triazolo-[5',1':3,4][1,4]-diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-18b :



(±)-18c

(*r*-11a,*c*-12,*c*-15,*c*-15a,*c*-16a)-2-Bromo-11a,12,15,15a,16,16a-hexahydro-12,15-methanobenzo[5,6][1,2,3]triazolo[5',1':3,4][1,4]-diazepino[7,1-*b*]quinazolin-11(9*H*)-one (±)-18c:





19

9*H*-Benzo[*f*]pyrimido[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepin-11-one 19: